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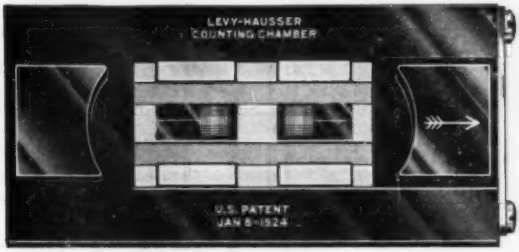

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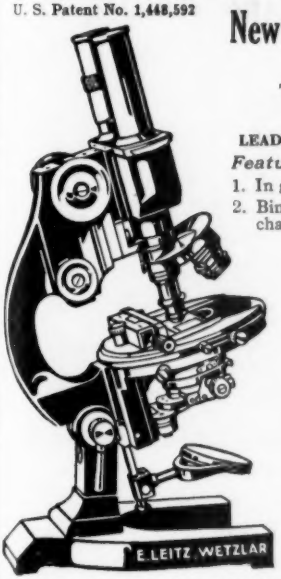

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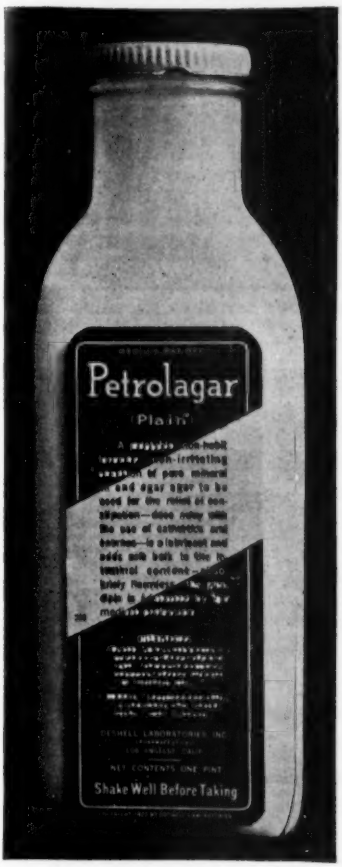

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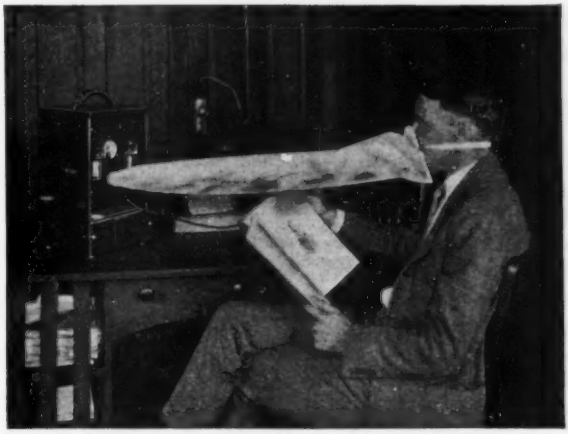

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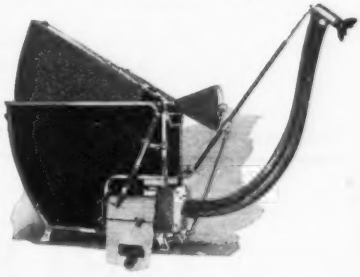

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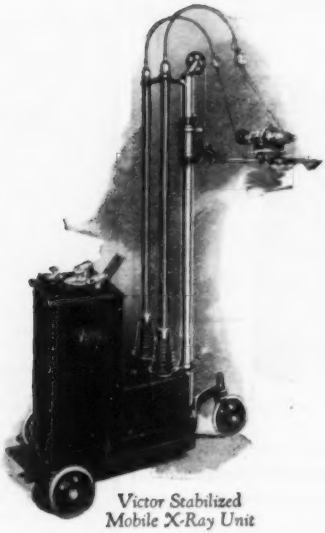

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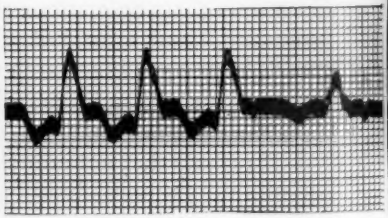

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OF THE MEDICAL SCIENCES

NOVEMBER, 1924

ORIGINAL ARTICLES.

ENDOCRINOLOGY FROM THE POINT OF VIEW OF THE SURGEON.*

By G. W. Crile, M.D.,

CLEVELAND CLINIC, CLEVELAND.

The surgeon sees the organs of internal secretion in three aspects: (1) When the incidence of some disease of the endocrine organs themselves, such as a malignant or benign growth or an infection, demands operative intervention; (2) when a hyperactivity of the gland is causing such destructive changes in the organism as to require the diminution of the secretion by partial extirpation; (3) when it is necessary to protect an organism stressed by the disease of some other part from the stimuli which may cause a hypersecretion of one or more of the endocrine organs. All of the endocrine organs, with the possible exception of the pineal, have this in common—that a hypersecretion may safely be corrected by the extirpation of a portion of the gland and that a hyposecretion may be compensated by the administration of the essential element in the secretion.

The first surgical removal of any of the endocrine organs—a thyroidectomy—was performed by Kocher in 1878, twenty-two years after Moritz Schiff had proved that the excision of the thyroid gland in dogs was invariably fatal. Kocher found that, although death did not follow complete extirpation of the gland in humans, a condition which he designated as "cachexia strumipriva" did follow. Following Kocher's observations, Schiff continued his

* Read before Section N of the American Association for the Advancement of Science, Cincinnati, December 29, 1923.

observations on dogs, and found that the symptoms which followed complete extirpation of the gland could be prevented by thyroid therapy—a graft of the gland into some part of the body, injection of thyroid juice or the ingestion of thyroid gland.

Horsley, von Eiselsberg and others confirmed the observations of Kocher and the experimental findings of Schiff, and as a result Kocher soon modified his operation so as to leave *in situ* a portion of the gland. Just when the first removal of a portion of a gland in the treatment of hyperthyroidism was done I do not know, Kocher's original thyroidectomies having been performed for the removal of the unsightly huge tumors of such common occurrence in Switzerland. Partial thyroidectomy for hyperthyroidism, however, was an obvious and logical sequel of the experimental and clinical work of the men mentioned above, as has been the development of experimental and clinical studies of modifications of other organs of internal secretion.

It is not necessary to more than cite the association of certain investigators with these later studies. Thus, for example, Halsted is associated with the identification of the cause of tetany following parathyroidectomy; Halsted and Cushing with surgery of the pituitary body; Batty with the first removal of the ovaries for a general somatic condition; Dandy with the first operative approach to the pineal body; Cannon, Stewart and Rogoff, Hoskins and others with the effects of experimentally induced variations of adrenal activity; Marine, Kendall, the Mayos and others with experimental studies on the surgery of the thyroid gland. While the pancreas, spleen and, to some extent, the intestinal mucosa may be included among the endocrine organs, their surgical significance need not be considered in this connection. The thymus also is omitted from this discussion, since its activity may be controlled by radiation.

The modification of the symptoms of hyperthyroidism by partial thyroidectomy, and the reciprocal interrelation of such kinetic conditions as emotional stress, physical exertion, chronic infection or physical trauma, with the effects of increased thyroid secretion, and of increased adrenal secretion, led me some years ago to look upon a certain group of diseases which are almost invariably associated with excessive emotion or physical strain, infection, autointoxication, etc., as kinetic diseases, since in them there exists a diminished or an excessive activity of some one or more of these glands of internal secretion. Such conditions are nervous exhaustion, neurasthenia, hyperthyroidism, myxedema, adolescent goiter, cardiovascular disease, diabetes, Bright's disease, apoplexy, acute acidosis, thromboangiitis obliterans and certain cases of epilepsy. An attempt was made, therefore, to discover whether or not by lessening the activating secretions from the thyroid gland and the suprarenals some of these conditions might be controlled. Twenty-

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four operations were performed, each of which included the division of one of the cervical sympathetics, adrenalectomy on the opposite side and partial thyroidectomy. In some, in addition, the other cervical sympathetic was excised. These operations include 13 for epilepsy, 4 for neurasthenia, 2 for diabetes, 3 for cardiovascular disease and 3 for thromboangiitis obliterans. Four cases of epilepsy showed very material improvement, and in certain other cases there was a temporary amelioration of symptoms, but, with the exception of one case of epilepsy, no permanent results have been achieved. In one case of apparently intractable diabetes there was a dramatic fall in the glycosuria on the day following the first operation, a fall which was maintained for a prolonged period, but as the patient was undergoing the Allen treatment at the same time the influence of the operation is debatable. In the control of the kinetic syndrome which we designate as hyperthyroidism, however, the role of the thyroid secretion is unquestionable, as is the role of partial thyroidectomy.

One peculiarity of each of the glands of internal secretion appears to be the power of influencing profoundly the entire organism, and many investigations have been undertaken for the purpose of identifying the specific manner in which the influence of each is manifested. Our own experimental investigations as to the nature of the special role played by the thyroid and the adrenals has led us to assign to these glands the title of *activators*, since we have found that adrenalin alone and thyroid secretion alone produce nearly all the symptoms produced by any cause of increased activation. Each causes increased metabolism; each causes increased activity of the other; each causes increased blood-pressure, increased pulse-rate, increased respiration, leukocytosis, sweating, dilation of the pupils, diversion of the blood to the surface, lowering of the threshold at the myoneural junction; each causes an early hyperchromatism of the brain cells followed by a chromatolysis if its administration is continued. When either is removed entirely the brain cells degenerate; the power to fabricate heat and mental action is progressively lost; after adrenalectomy death soon follows; after thyroidectomy life continues only in so far as it is expressed by a continued heart action; a sluggish circulation; an impersonal existence.

The fact that the essential content of the thyroid secretion is iodin and that iodin increases electric conductivity, together with our histological studies, led us to believe that the action of the secretions of these glands was electrical in character. In the course of certain biophysical researches, therefore, we found that in an iodized animal, whether iodized directly by the injection of iodoform or by feeding with thyroid extract, the electric conductivity of the brain was uniformly increased. In cases of protracted iodism, however, when the animal was in a state of exhaustion the

conductivity was decreased. Identical changes in the conductivity of the brain followed the administration of adrenalin, a single injection being followed by an increase in the conductivity of the brain; repeated doses by a decreased conductivity of the brain. In each instance the liver showed changes in the opposite direction from those in the brain. That is, when the conductivity of the brain was increased during the stage of increased activation the conductivity of the liver was decreased, the opposite being true in the stage of exhaustion from either cause, that is, when the conductivity of the brain was decreased the conductivity of the liver was increased. These findings produce a powerful link in the chain connecting these two organs, not only with each other but with the brain and the liver.

In view of our histological findings in which, as stated above, the administration of either thyroid extract or of adrenalin was followed by an immediate hyperchromatism of the brain cells, with a later increased chromatolysis when the administration of either thyroid extract or adrenalin was continued, together with the corresponding changes in the electric conductivity and the findings in other experiments which link as irrevocably as these findings, the histological picture with the electric conductivity, we made an attempt to interpret the hyperthyroidism or hyperiodism, or adrenalism, in electrical terms. As further evidence to this end we made investigations to discover whether or not temperature changes were produced in the brain by adrenalin alone and by adrenalin in an iodized animal. We found that invariably the injection of adrenalin in the normal animal was followed by a characteristic increase in the temperature of the brain amounting to about 0.5° C., the period of rise and fall being usually about ten minutes. In an iodized animal, on the other hand, the injection of adrenalin produced an abrupt rise in the temperature of the brain, in some instances amounting to from 1.5° to 2° C., with as abrupt a return to below the normal temperature. Thus, again in these findings adrenalin and the essential element in the thyroid secretion prove their interrelationship and their essential effects upon the activity of the brain. It was significant that with the exception of the thyroid the temperature of no other organ or tissue was increased by the injection of adrenalin.

The effect of the normal adrenalin secretion upon the brain was dramatically shown by observing the temperature of the brain during asphyxia. As Cannon has shown, during asphyxia there is an increased output of epinephrin. During asphyxia the temperature of the brain shows the characteristic adrenalin curve. In a thyroidectomized animal the response of the brain to adrenalin was far less than in an animal with an intact thyroid.

Summary. The results of these studies, therefore, have provided fundamental evidence in favor of the theory that thyroid secretion

and epinephrin are essential elements in the operation of the electrochemical mechanism which we conceive the human organism to be; and that in the operation of the electrochemical mechanism the thyroid and the adrenals are indissolubly linked with the brain and the liver, their probable role being, as shown by these temperature studies, to control the oxidation within the brain whereby the electric charges which operate the mechanism are accumulated. The practical surgical bearing of these studies is that they point the way to an increased control of the factors which make or mar the surgical results.

If the oxidation which controls the activation of the brain is in turn controlled by the secretion of the thyroid and of the adrenals, then by so much as the activity of these secreting glands can be controlled by management, technic and environmental control, by so much will the hyperactivity of the brain be prevented and the organism conserved.

The proof that this assumption is correct is shown by mortality percentages and by morbidity results; since our efforts have been directed to the control of those factors which increase the activation of the organism, the mortality rate in the last 1000 thyroidectomies for hyperthyroidism has fallen to 0.8 per cent. In the last 720 bad-risk cases of hyperthyroidism it has been 1.2 per cent. Moreover, the same measures in acute abdominal risks of all kinds have reduced the mortality to 3.8 per cent. Our belief is that to the extent to which the activation of the organism can be depressed, to that extent will the organism be conserved.

THE DIAGNOSIS AND TREATMENT OF EXOPHTHALMIC GOITER (GRAVES' DISEASE).*

By J. William Hinton, M.D.,
NEW YORK.

(From the Goiter Clinic of Dr. Charles Gordon Heyd at the New York Post-Graduate Medical School and Hospital.)

A review of the cases of exophthalmic goiter (Graves' disease) admitted to the Goiter Clinic of the New York Post-Graduate Medical School and Hospital during the past two years, numbering 20, showed that the previous treatment consisted of:

1. *Physiological Rest, with Correction of Foci of Infection.* Two cases fell in this group. One had been under treatment for two

* I am greatly indebted to Dr. Heyd for the privilege of using the records of these cases in this review.

and a half years and 1 for one year. The patients were unable to work when seen.

2. *Roentgen-ray Therapy.* This group included 4 cases. They had had from four to ten roentgen-ray treatments. None of these patients were able to work.

3. *Radium Therapy.* Two cases were in this group. The first patient, who had had ten radium applications, was doing light work, but did not feel normal and his basal metabolism was 25+. The second patient showed a clinical picture of myxedema after eight applications, but did not return for the basal metabolism test. Follow-up letters were unsuccessful in getting the patient to return for treatment.

4. *Ligation of Superior Thyroid Arteries.** This series included 2 patients who had had their ligations performed five and six years previously. One patient was blind from corneal ulceration, and was 65 pounds under weight, after ligation of the superior thyroid arteries. The other was 50 pounds under weight, and was able to work only about eight months during the year after ligation of both superior and one inferior artery.

5. *Gynecological Treatment.* This group numbered 2. One had been operated on for displacement of the uterus, and three months later was operated for exophthalmic goiter. The other patient had had office treatment for uterine displacement for several weeks, and was operated upon one year later for Graves' disease. These cases gave an irregular menstrual history.

6. *Incomplete Surgery.* One case came under this heading. Four years before admission to Clinic the patient was operated upon, and had one lobe of the thyroid gland removed. The symptoms returned one year later, and the patient was then treated with injections of boiling water, without relief.

7. *By Ophthalmologist.* One case. This patient had a unilateral exophthalmos of several months' duration, and it was thought he had an intraorbital tumor. Roentgen-ray therapy was advised and given.

8. *By General Medical Treatment with Sedatives.* Six cases. These cases had been under medical care varying from three months to seven years. It is needless to say that these patients received only temporary improvement, or they would not have consulted a surgical clinic for their condition.

The Signs and Symptoms of Graves' Disease. The cardinal signs and symptoms of Graves' disease are: (1) Tachycardia; (2) tremor; (3) exophthalmos; (4) enlargement of the thyroid.

The secondary signs and symptoms are palpitation, insomnia, loss of weight, gastrointestinal disturbances, pigmentation and itching of skin, hyperhydrosis of hands and feet, disturbance of the

* The cases of this group, 1 of Group 5 and 1 of Group 8, are from my personal records.

menstrual function, flushed and warm feeling, emotional and irritable state.

The first positive findings are tachycardia and tremor. Tachycardia is a constant finding in these cases, and it is due to the selective action of the thyroxin on the accelerator nerves of the heart. The pulse does not become normal during rest in bed or while asleep. In the neglected cases there is an arrhythmia, which is a bad prognostic sign, as it indicates marked cardiac degeneration. Tremor is one of the earliest symptoms. The characteristic feature is its very fine type.

Exophthalmos is present in 85 per cent of the cases. It is not always present in the early stages of the disease, and may be unilateral in a small percentage of cases. Cases of several years' duration may give a history of intermittent exophthalmos. The exophthalmos seems to bear a direct relation to the cycles of thyrotoxicosis. It may entirely disappear during the interval between crises. It is due to the spasm of Landstrom's and Müller's muscles, both of which are innervated from the cervical sympathetic system. Dalrymple's sign is usually seen very early. This is a widening of the palpebral fissure. Von Graef's and Kocher's signs are present in the early cases. A lack of the upper lid to follow the globus oculi on looking down constitutes the former sign, and the same on looking up the latter sign. Stellwag's sign—a lack of winking, which is normally from three to five times per minute—is very variable and of little diagnostic value. Moebius' sign—lack of convergence of the eyes when looking at a fixed point—is also variable. Wood[1] states that dryness of the eyes is a common complaint in cases of Graves' disease. Dalrymple's and von Graefe's signs are due to spasm of Müller's muscle which runs from the superior palpebræ levator muscle to the tarsal cartilage.

The enlargement of the thyroid may not come on for a considerable period after other cardinal signs of Graves' disease, and is present in about 80 per cent of the cases. It is very variable, and may be present early or not until the disease is well developed. The enlargement is frequently intermittent and is directly related to the crises of the disease. At first there is a soft enlargement which becomes elastic as the disease progresses; in neglected cases it has a firm consistency. On palpation the thyroid gives a definite pulsation, and auscultation gives a bruit. This bruit has been described by Riesman,[2] and may be heard on auscultation over the eye. These cases, if neglected, undergo a fibrous tissue replacement and go over into the "burned-out thyroid" of Crotti,[3] with a diminished secretion and, finally, myxedema.

The Secondary Signs and Symptoms of Graves' Disease. The most important is the loss of weight, which is very marked in the severe cases, and may amount to 40 or 50 pounds during the crisis of the disease. In the interval between the crises the weight may

become normal; some remain constantly under weight. One case in this series did not lose weight, but gained about 30 pounds during the first year of the disease.

The gastrointestinal disturbances are variable; a ravenous appetite is the rule in cases with marked loss of weight; anorexia is not uncommon. The case with marked gain in weight had anorexia. Diarrhea occurs occasionally in the severe cases, and is very annoying to the patient. Palpitation comes on in spells, and is quite frequently worse at night. It is a factor in causing insomnia. Insomnia is usually present in these cases, but they respond to almost any form of sedative.

The menstrual cycle in these cases is always irregular; the periods may be delayed and the flow very scant. In later cases amenorrhea may be present, this disturbance in the menstrual cycle being the reason for consulting the gynecologist. Loss of libido is also a frequent complaint. The heat production in these cases is greatly increased from the excessive protein destruction. The patients wear very few clothes in cold weather and are uncomfortable from heat in surroundings which the average individual finds comfortable.

Pigmentation of the skin is very frequently seen around the eyes and on the forearms. The skin may also be easily irritated by heavy clothing. Hyperidrosis of hands and feet is very annoying when present. The emotional and irritable state of these patients makes them very trying to live with.

The only laboratory data which have a definite place in the diagnosis and treatment of Graves' disease are the basal metabolism determinations. The basal metabolism is of value in diagnosing the early cases from colloid goiters with a psychoneurosis. In the former it is always elevated, but never in the latter condition. The basal metabolism has also a definite place in selecting the type of treatment to be employed, as well as in determining the prognosis. These cases go through cycles of thyrotoxicosis, and if the metabolism does not drop with conservative treatment the patient is in the ascending wave of the crisis, and any surgical procedure at this time is contraindicated. A metabolism of 60 or 65 + that will drop 10 to 15 points with rest in from seven to ten days gives a much better prognosis that a metabolism of a 40 +, which remains stationary during the same period. The Goetsch test is not usually employed in the diagnosis of Graves' disease at the present time, since it is liable to have a very deleterious effect on the patient, due to the action of adrenalin on the sympathetic nervous system, which is hypersensitive in this condition.

The urine analysis in these cases shows quite frequently a glycosuria. This is due to the fact that the pancreas and the thyroid have an inhibitory action over each other, and in hyperthyroidism the pancreas is inhibited to such an extent that carbohydrate metabolism is incomplete; likewise there is a hyperglycemia. The sugar

tolerance test is of neither diagnostic nor prognostic value. The differential blood count will show a diminution in the polymorphonuclear leukocytes and an increase in the number of lymphocytes. The number of leukocytes usually stays within normal limits. The diminution in the polymorphonuclear leukocytes is supposedly directly related to the severity of the toxemia.

The Clinical Tests. The blood-pressure is normal or diminished. This is due to the action of the thyroxin on the vasodilator fibers of the arteries. The Katzenstein test consists in taking the pulse and blood-pressure and then compressing both femoral arteries for one minute; if the heart has no myocardial degeneration the blood-pressure should rise and the pulse fall; the heart with slight degeneration will give a normal blood-pressure and pulse; in marked myocardial degeneration the blood-pressure drops and the pulse goes up. It is variable and of little prognostic value.

Treatment. The advice this group of patients had received depended entirely on the specialist seen, and each patient had been assured of relief by the method of treatment employed. Each patient had been definitely advised against surgery.

It is very important that these patients should be under the supervision of that group of men who afford the highest percentage of relief, namely, the surgeons. Falta and Meyers[4] state that "roentgen-rays and radium usurp the field that was formerly accorded to purely medical treatment. For the time being, at least, the surgeon, as opposed to the radiologist, seems to have the better of the argument."

A very small percentage of these cases can be cured by medical treatment, but it is only in selected cases in which prolonged medical treatment promises satisfactory results, and with only those patients who can financially afford prolonged rest, without nervous tension, should this be undertaken. Roentgen-ray and radium have not given satisfactory results in the treatment of this condition. At present one cannot regulate the proper dosage, for too many or too few cells are killed, and the relief is either only temporary or the patient goes over into a state of diminished thyroid secretion with the clinical picture of myxedema, which is not an uncommon occurrence. In severe cases it should never be employed because thyrotoxicosis is quite frequently produced, with a fatality. Among the German surgeons the consensus of opinion is against the use of roentgen-ray in this condition. The serum from thyroidectomized sheep—Moebius' serum—has not given the results expected. The same can be said of the Rogers-Beebe thyroid residue.

So far, surgery offers the best means of restoring these patients to complete health, with the least financial loss and the lowest mortality rate. Surgery has given 80 to 85 per cent of cures in late cases, as against 20 per cent of cures by medical treatment.

These statistics are based on the fact that the surgical cases are usually taken from the ones that had not been improved by medical treatment and were turned over to the surgeon for relief.

Surgery should not be advocated in all cases when first seen. One may use conservative treatment for several weeks or several months before deciding to operate. The type of operation to be performed, whether ligation of the superior arteries or resection of the thyroid gland, will depend on the clinical picture, history and the basal metabolism rate. The preoperative treatment in these cases, with the selection of the proper surgical procedure in each case, is the main factor in reducing the mortality of this serious condition to about 1 per cent.

The preoperative routine used in this Clinic consists of repeated basal metabolism determination, with rest in bed; high carbohydrate diet, forced fluids; digitalis, mx, three times a day; luminal, gr. 1.5, every fourth hour; morphin, gr. 0.25, when necessary; Lugol's solution, m5, three times a day for ten days. Lugol's solution (Plummer) will change the type of secretion from that of Graves' disease to the form of a toxic adenoma, which is supposedly due to alteration in the formula of the thyroxin. This should not be employed longer than fourteen to twenty-one days. Following this procedure the metabolism will drop from 15 to 20 points in from seven to ten days in all cases not in the ascending wave of the disease. If they do not respond to the above routine they are in the crisis of the disease, and any surgical procedure is contraindicated at the time, and should not be undertaken until there is a marked drop in the metabolism.

Graves' disease has been produced by Falta and Meyers[5] experimentally in dogs and rabbits by the injection of thyroid extract, as well as by the extract of the struma removed in the operating-room. These animals have shown all the cardinal symptoms, as well as the histological picture of the disease.

The picture of Graves' disease has been produced in human beings by taking large doses of thyroid extract for the relief of obesity, with all the cardinal symptoms, including exophthalmos. This has subsided on discontinuing the medication, together with rest.

Crotti[6] has expressed the opinion that Graves' disease is due to a thyroneuropolyglandular condition, which is very true; but the thyroid gland is the chief factor at fault in the production of the condition, so the treatment should be directed at the thyroid gland instead of at the nervous system or at the other glands of internal secretion.

Conclusions. 1. Surgical treatment of Graves' disease has given a higher percentage of cures, with a lower mortality rate than the so-called conservative treatment.

2. Graves' disease has been produced experimentally in animals

from thyroid extract and the extract from the goiter removed at operation.

3. The review of this series would indicate a lack of coöperation by the various specialists in the treatment of this condition.

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EVIDENCE THAT IDIOPATHIC EPILEPSY IS A SENSITIZATION DISEASE.

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Recently Dr. Raulston and the writer made a report on the treatment of migraine by intravenous injections of a 5 per cent peptone solution. Evidence was presented at this time to support the view that migraine might belong to the sensitization group of diseases. Since the publication of this article the treatment has been employed in a considerable number of additional cases, with results that support our views expressed at that time—that such treatment has a distinct effect on the migraine seizures. The object of the present article is to call attention to the possibility that idiopathic epilepsy may fall in this same group.

Asthma, hay-fever, urticaria, a high percentage of eczemas and pruritus may be considered as due to sensitization or hypersensitiveness to protein. It is unnecessary to call attention to the varied clinical symptomatology in this group. They all have, however, several points in common, indicating the probable relationship of this group of diseases. Perhaps the most striking feature is their hereditary character, either the particular disease appears in the offspring or some other member of this group. Not infrequently one or more of these diseases appear in the same individual.

Nervous factors also play an important role in this group. This is especially marked in asthma, urticaria, migraine and epilepsy. Until comparatively recently asthma was considered a neurosis, and at present many physicians emphasize the importance of nervous influences. Urticaria and angioneurotic edema are clinically closely related. Foods that can be eaten with impunity may

excite an urticaria at periods when the patient is suffering from nervous strain. The importance of nervous factors in migraine or epileptic seizures is generally recognized. As a consequence of nerve strain the hypersensitiveness of the individual is apparently increased.

Migraine and epilepsy, like asthma, may first develop following some acute infection. Of the various acute infections thought to be responsible for the onset of epilepsy, scarlet fever is considered the most important. On the other hand, acute infections frequently exercise an inhibitory action on all this group. Asthma, which has proven resistant to all forms of therapeutics, including desensitization treatment, may temporarily disappear after a severe infection, as typhoid or pneumonia. No reference was found in the literature in regard to the effect of infections on hay-fever. Migraine very frequently will temporarily and sometimes permanently disappear after an acute infection, and this is also true of epilepsy. Tinel[15] refers to the disappearance of epileptic seizures after typhoid and pneumonia. Spratling reported that epileptics who acquire tuberculosis frequently show amelioration or disappearance of seizures. Turnowsky[11] refers to 3 cases of established epilepsy, in all of whom the seizures subsided—2 after pneumonia and 1 after scarlatina. Hamilton[10] reports 12 epileptics that acquired typhoid; 9 showed distinct improvement—1 of these was free from seizures after four years.

This improvement after infection might be explained on the basis of desensitization, as this is the accepted explanation in asthma.

Pregnancy not infrequently modifies asthma, migraine and epilepsy. All of these may subside temporarily during this period. On the other hand, they may first develop during pregnancy. Frank Coke[21] recently refers to an asthmatic who was entirely relieved during six pregnancies. There are many other references in the literature to the favorable effects of pregnancy on asthma. Weir Mitchell[22] reported that he had never seen epilepsy made worse by pregnancy—on the other hand, the seizures are often less frequent. Beraud[16] observed the effect of pregnancy on 31 epileptics—8 were influenced unfavorably and 15 favorably. In 8 of these the seizures entirely disappeared during this period. As the placenta behaves as a foreign protein to the mother, it is possible that desensitization might result.

The above evidence is merely suggestive that migraine and epilepsy may be sensitization diseases. There is considerable therapeutic evidence to support this view. It has been reported especially by French physicians that after treatment for rabies, or after the use of diphtheria antitoxin, epileptic seizures have temporarily disappeared. Bouché and Hustin,[23] following this lead, treated a number of epileptics with normal horse serum with encouraging results.

Spangler's[2] use of snake venom in epilepsy, reported in 1908, in the light of recent developments deserves consideration. He was led to try this treatment after reading a report where a patient who had been subject to epileptic seizures for fifteen years had remained free for two years after being bitten by a rattlesnake. Snake venom contains both a poisonous peptone and a globulin. The peptone is largely a nerve poison; the globulin lessens blood coagulability and increases vessel permeability. As there was a theory at this time that the epileptic seizure was associated with increased blood coagulability, he ascribed his good results to modification of blood coagulation. His report on 36 cases treated by subcutaneous injections of crotalin showed that every patient was affected favorably, although in some instances the improvement was very slight, in others the seizures became infrequent, or the major attacks entirely disappeared. Three patients had been entirely free for two years or more and 2 for eighteen months. In some cases the seizures permanently disappeared after the first series of five to six injections. He advised, however, that after the first series the injections be continued at intervals of two to four weeks. This is strikingly in accord with our observations in the peptone treatment of migraine. Spangler's treatment appeared so irrational that no attempt was made in this country to verify his results. In France, however, reports have appeared from time to time recording the value of this treatment.

Held[3] recently made a report on 400 cases of epilepsy treated with serum of animals previously injected with serum and spinal fluid from epileptics. He states that 18 per cent of his series had been free from seizures two to four years and only 30 per cent were not benefited. If there is any value in this treatment it is probably due to the effect of normal serum rather than to changes produced by previous treatment of the animals.

Lion,[24] in 1911, reported good results in epilepsy from injections of brain extract.

All of the above methods of treatment can properly be classed as protein therapy. Whether the results were due to non-specific desensitization or some other action of protein is a matter to be determined.

Recently two reports have been made by English physicians, which lend support to the above reports, or, at least, suggest that foreign protein injections can modify epilepsy. James Crockett[12] conducted a tuberculosis sanitarium where all patients received tuberculin. He observed that in case the patient, in addition, had epilepsy, the seizures usually disappeared. He then treated 23 cases of epilepsy with tuberculin injections, beginning with 0,000,000,01 cm., and gradually increasing the dose, never exceeding 0.4 cm., and always endeavoring to avoid a reaction. A total of eight to ten injections were given at approximately weekly intervals.

Eleven patients in this group, at the time the report was made, had been free from seizures for three months or more. One patient who had 309 major and minor seizures in the month preceding the treatment had been entirely free for nineteen months.

Almost simultaneously with this report there appeared in the *British Medical Journal* a brief article by Edgeworth.[1] He treated 20 epileptics with intravenous injections of a 5 per cent solution of peptone, beginning with 5 minims and gradually increasing to 20 minims. Nine of these patients had been at least temporarily benefited.

The above therapeutic evidence cannot safely be ignored. The question arises, What is the method of action of these various agents?

If we permit ourselves to assume that the epileptic seizure is an anaphylactic manifestation, it raises the question of possible non-specific desensitization. There appears in the literature an occasional reference to a specific food being responsible for the seizures. Others refer to the effect of diet upon the seizures. These isolated reports that food may play a role in the seizures are significant if not convincing. The most interesting investigation of this phase of the subject has been reported recently by Wallis and Nicol.[17] They made protein skin tests on 122 insane epileptics; 46 of these gave positive reactions; 28 reacted to peptone, 15 to cereals, 15 to fish and meat, 9 to vegetables, 9 to eggs and 3 to milk. One hundred controls were tested in the same manner; 13 of these were normals, 70 dementia precox and 17 various other forms of insanity. Only 4 gave a positive reaction—all to peptone and all in patients with dementia precox. In case the test was made just previous to the seizure the patient might react to a number of proteins, although earlier he may have been sensitive to only one. Following a seizure all tests might become negative. This desensitization corresponds to the antianaphylactic state observed in animals after anaphylactic shock. On account of this period of desensitization they emphasize the importance of making the tests several days after a seizure.

In those sensitive to a particular food the withdrawal of this article from the diet was followed by striking improvement, the seizures entirely disappearing to return again in case the offending food was taken. This report furnishes the necessary evidence that in some cases of epilepsy food sensitization is responsible for the seizures. The objection might be raised that if food sensitization was an important etiological factor in epilepsy it would long ago have been recognized. It is well to recall, however, that only in recent years has asthma been considered a sensitization disease.

The work of van Leeuwen and Leydner[4] furnishes some additional support to the sensitization theory, using a method first proposed by Freund for isolating a muscle-stimulating substance from the blood. They were unable to detect this substance in the blood of

normal individuals. They then attempted to isolate it from the blood of patients suffering from a variety of diseases. They found it present only in the blood of patients with asthma, urticaria, migraine and epilepsy. It is their opinion that this toxic substance is in some way related to their "allergic disposition." If these results are confirmed it would at least indicate a close relationship between this group of diseases.

There is considerable evidence that there is a non-specific desensitization. This subject was briefly discussed in our article on migraine. Longcope[13] recently reviewed this subject. He states: "It seems impossible to avoid the conclusion that in animals sensitized to two proteins anaphylactic shock to one reduces temporarily the sensitiveness to the second." All admit that it is not as complete or as lasting as specific desensitization. Larson[18] has recently reported he was unable to desensitize with peptone animals sensitive to egg albumen. This work, however, can scarcely be accepted as disproving non-specific desensitization. In addition to the laboratory experience on this subject there is considerable clinical evidence supporting the non-specific theory.

Frank and Strouse[19] treated hay-fever patients with autogenous staphylococcus vaccines, and reported results that compare favorably with pollen therapy. Sutton, in a recent personal communication stated that during the past summer hay-fever patients who were not relieved by attempts at pollen desensitization obtained temporary relief after intravenous typhoid vaccine. These results are in accord with the observation of Rosenau and Anderson, that animals receiving repeated injections of foreign protein became highly insusceptible to anaphylactic shock. van Leeuwen and Varakamp[7] report 2 patients relieved of hayfever following treatment with tuberculin. Rachmann[5] has recently stated that he considers the treatment of asthma with bacterial vaccines as non-specific. Schottmüller[8] reports 8 patients with bronchial asthma treated with intravenous non-specific vaccine; 7 of these were relieved of their asthma. It is safe to state that it has not been clearly demonstrated that autogenous vaccines are superior to stock preparations in treating the bacterial type of bronchial asthma. For several years we made it a routine practice to give all bacterial asthmas entering my service at Cook County Hospital two or three intravenous injections of typhoid vaccine. An occasional patient was promptly relieved. Those not benefited were treated with autogenous vaccine. In no case, however, that had failed to be relieved by the typhoid vaccine was there any benefit from autogenous vaccine.

van Leeuwen and Varakamp[7] have recently reported on the use of tuberculin in asthma. They selected only those patients who gave a positive von Pirquet. It would be interesting to see, however, whether the result would not have been just as satisfactory

in those patients in which the test was negative. They used Koch's T.O.A. in doses, ranging from 1 cm. of a 1 to 100,000 solution, gradually increasing, but not exceeding 1 cm. of a 1 to 10,000 solution, and always endeavoring to avoid a reaction. If the dose was too large an asthmatic seizure was precipitated. Twenty-eight patients were included in their series. All gave negative or, at most, slightly positive protein skin tests, and were probably chiefly the bacterial type of bronchial asthma. They report 68 per cent completely relieved, 10 per cent greatly benefited, 18 per cent decidedly improved and 4 per cent not benefited. These results compare very favorably with those obtained by specific desensitization. Auld,[6] following the suggestive animal experiments of Dale and Kellaway, demonstrating that peptone would prevent anaphylactic shock in guinea-pigs, undertook the treatment of asthma with intravenous peptone solution. All types of bronchial asthmas were included in his series. No actual figures were given in regard to the percentage relieved, but he reports he was highly pleased with the results. Patients with cat or dog asthma were relieved while still in contact with these animals.

The above clinical observations support the laboratory experimental work that desensitization is not strictly specific. This enables the physician to apply a therapeutic test in diseases where hypersensitiveness may be a factor. Recently a patient with a long-standing intermittent hydrarthrosis came under my observation through the courtesy of Drs. Plummer and Lewin. The precise periodicity of the seizures in many cases of this disease excited the suspicion that the trouble might be anaphylactic in character. This exact periodicity is occasionally observed in migraine. This particular patient developed his trouble every thirteen days. In reviewing the literature on this subject Bierring[20] reports that in 8 out of 9 patients with this trouble, who became pregnant, the seizures disappeared. This patient was first given peptone. As it excited a marked urticaria, typhoid vaccine intravenously was then used, the patient receiving about twelve injections. He has now been free from his trouble for eight months, although in his last report he states that he has recently had periodical stiffness of the knee, but no swelling, and has been advised to take a few more treatments.

My own experience in treating epilepsy by this method is too limited to be of value. Colleagues, however, have reported to me most satisfactory results both with peptone and tuberculin, confirming the work of Crockett and Edgeworth.

Summary. The clinical results reported in epilepsy should stimulate further investigation, both in regard to sensitizing agents and non-specific therapy, and it is the object of this presentation to create an interest in this subject. It is to be remembered that in recognized sensitization diseases, such as hay-fever, no one has

been able to secure anywhere near 100 per cent of cures. For this reason failures must be expected. It is also to be borne in mind that desensitization is not permanent—the treatment must be repeated at intervals in order to avoid recurrence.

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SOME CARDIAC EFFECTS OF ATROPIN.

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Every medical man knows that atropin tends to hasten the heart's action, the pharmacological explanation being that it paralyzes the vagal nerve-endings in the heart, and thus allows that organ to run riot. The dose of the drug that is required to fully throw the vagus nerve out of action is at least $\frac{1}{50}$ gr., and in many people as much as $\frac{1}{33}$ gr. or even more is necessary.

The effects of many drugs vary not only in quantity but also in quality with the dose given, and atropin is a good example of the latter, in that the action of a small dose is the very opposite of that from a larger one. If a sufficiently small amount be administered

no hastening of the heart occurs, but rather a slowing, and it is with this slowing action that we are now concerned. Many books on pharmacology do not even mention this slowing, while a few do so in a casual way. Thus, A. A. Stevens[1] writes, "Prior to the acceleration (of the heart) there is occasionally some slowing from stimulation of the inhibitory center in the medulla, but this effect is always transient." But what we desire to show is that if the dose be sufficiently small this preliminary slowing is not transient, but lasts for many hours, and is the *only* effect of the drug on the heart-rate.

Petzetakis[2] demonstrated that there are two stages in the action of atropin on the vagus: (1) The one of vagal excitability, and (2) the one of vagal paralysis. In the first stage the heart tends to slow and a degree of heart-block may occur and extrasystoles appear; in the second stage the heart hastens and any block tends to lessen or disappear. With a large dose the first stage is transient and quickly followed by the second.

Until a couple of years ago our opinion of the action of atropin on the rate of the heart was the same as that of O. T. Osborne,[3] who in his book says, "Atropin causes increased rapidity of the heart, raises the blood-pressure. The average dose is $\frac{1}{100}$ gr." After the work which is described below we now agree with V. E. Henderson,[4] when he writes, "The normal therapeutic dose of atropin slows the heart centrally; the vagal endings are not paralyzed," and with H. McGuigan,[5] when he says, "Small doses of atropin, if they influence the heart-rate, only slow it."

At that time one of us got several house physicians and senior students to try the drug in doses of $\frac{1}{100}$ gr. on patients and on themselves, and the results were either negative or else the heart was actually slowed. We thought that perhaps the drug was at fault, so tried the triturates of several makers, but always with the same results. When we used $\frac{1}{50}$ gr. or more the pulse hastened, and, by the way, the blood-pressure, both systolic and diastolic, tended to be lowered and never to be raised, most books to the contrary. We also noticed that even after large doses the heart was at first slowed, although it quickly then hastened, following exactly Petzetakis' two stages.

The matter seemed to be worthy of further and more systematic study, and during the past year we have tried the effects of small doses of atropin upon many healthy individuals and also on a certain number of abnormal people, nearly 100 people in all. The work was done in several stages.

1. Single doses of $\frac{1}{100}$ gr. were given hypodermically or by the mouth (the effects are the same by either route, but rather slower when the drug is given *per oram*). Nearly always the pulse-rate fell considerably and, further, stayed down for several hours. Fig. 1 shows this and also the lowered blood-pressure.

2. Next we tried the action in a different way. In some 50 individuals (many being medical students) the pulse was taken every hour or so for one day, in order to get the usual rate for the individual. Next morning $\frac{1}{100}$ gr. of atropin was given by the mouth, and the pulse counted in the same way. On the third day the rate was again taken. On the day on which the atropin was taken the average pulse-rate was nearly always lower, often by as much as 8 to 10 beats per minute. The average for the whole group was as follows: First day, −80.22; second day (atropin), −75.5; third day, −80.45.

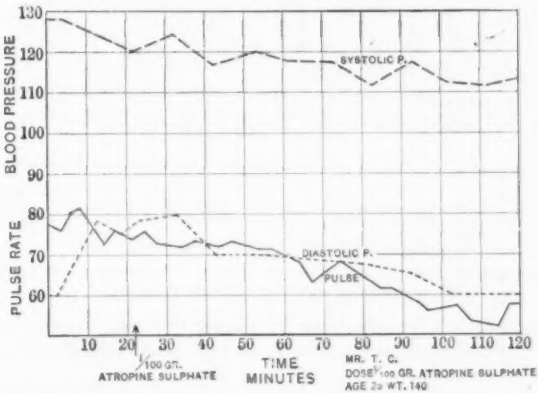

FIG. 1.—Slowing of pulse-rate and lowering of blood-pressure after $\frac{1}{100}$ gr. of atropin sulphate.

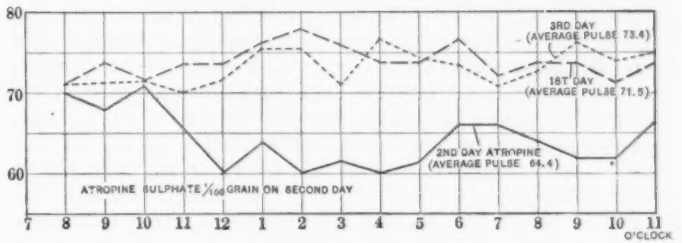

FIG. 2.—Pulse on three consecutive days. On second day $\frac{1}{100}$ gr. of atropin sulphate given and pulse slowed.

The slowing of the rate persisted for many hours, and often lasted all day after the dose given at 8 A.M. In a few instances there was little or no slowing or even a slight hastening. To such people a smaller dose was subsequently given, and in nearly every instance the heart was slowed. Evidently some people are more susceptible to the drug than are others. The average fall in our

series was not very great on account of these susceptible cases. Fig. 2 shows a typical finding.

The pulse on the atropin day was considerably lower than on the day before or the day after.

In another case (Fig. 3) $\frac{1}{50}$ gr. was given on the second day, and produced a preliminary slowing followed by a considerable rise which was succeeded by a prolonged slowing, as the dose in the blood diminished.

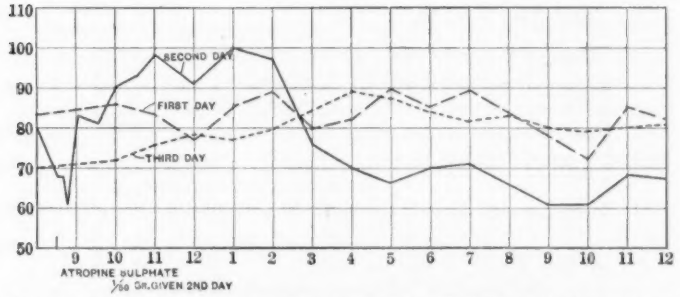

FIG. 3.—Atropin sulphate, $\frac{1}{50}$ gr., given by mouth. Preliminary slowing of heart, then hastening and final prolonged slowing.

3. If atropin in small doses increases the vagal excitability it should tend to enhance the effects of any other stimulation of the nerve.

Petzetakis found this to be the case in regard to ocular pressure. Pressure on the eye-balls tends to slow the heart reflexly through the vagus. If it be done in animals or in persons who have had preliminary small doses of atropin the effect is much more pronounced than usual. In the same way as digitalis somewhat slows the regular heart through the vagus, one would expect to see that when it is given in conjunction with small doses of atropin the slowing effect would be greater, and this we find to be the case. A number of individuals were put upon a dram of tincture of digitalis for a week, and it was found that the heart was very slightly slowed. Then a single dose of $\frac{1}{100}$ gr. of atropin sulphate was given, and the slowing became very much exaggerated, being in some instances as much as 40 beats per minute. Both the drugs were acting by stimulating the vagal centers. Fig. 4 shows such a case. The upper tracing gives the effects of atropin alone, the lower the effect of the same dose given after the individual had been on a daily dose of 1 dram of tincture of digitalis for a week. In this case when the pulse became very slow some degree of heart-block occurred. The amount of digitalis given would not likely of itself have produced any heart-block, but the combined effect of the two drugs did so. This fits in with J. T. Halsey's[6] results,

where in dogs in which he had produced partial heart-block, by the use of digitalis or strophanthin, atropin in small doses increased the block.

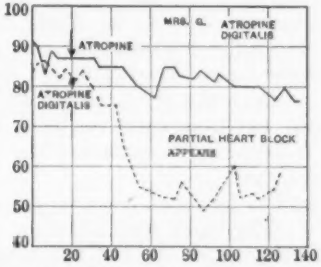

FIG. 4.—Digitalis and atropin. Upper tracing shows effect of atropin alone. Lower tracing, of atropin after a week of digitalis. Same individual.

4. If atropin in small doses increases heart-block due to digitalis, then one would expect to find that it would act similarly in block caused by other factors. We found this to be the case in several patients, of which the following is an example:

CASE HISTORY.—Miss A., aged twenty-eight years, had partial heart-block of unknown origin and of years duration. Auricles were beating regularly at 60 per minute; ventricles irregular, run-

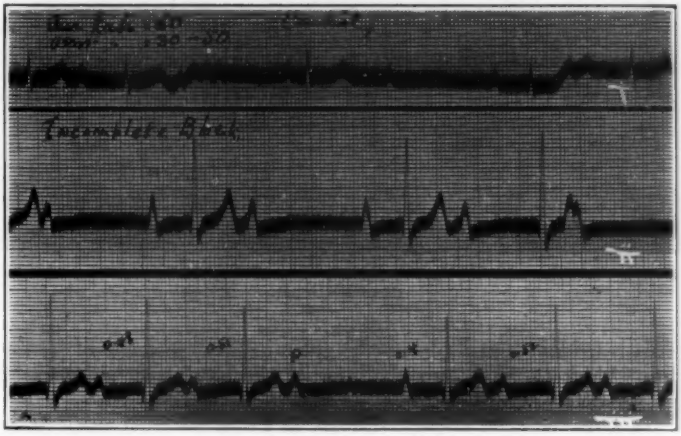

FIG. 5.—Partial heart-block.

ning at 30 to 50 per minute, due to occasional missed beats; P–R interval long, varying from 0.4 to 0.52 (Fig. 5). After exertion, such as from sitting up in bed, the pulse became regular and the

auricular and ventricular rates the same, but the *P–R* interval remained long (0.41 to 0.48). She was given $\frac{1}{50}$ gr. of atropin hypodermically. Five minutes later the block had increased, and the *P–R* interval was as much as 0.64. Thus, the first effect of the drug was to increase the block. Forty minutes after the atropin had been given the condition had changed, and now the auricles and ventricles were both beating at the rate of 70 per minute, and the *P–R* interval was reduced to 0.37. Thus, the first effect of the atropin was to increase the block by vagal activity, but this was soon followed by a decrease of the block as the vagal endings became paralyzed.

Next, this patient was put upon doses of $\frac{1}{200}$ gr. of atropin by mouth thrice daily. The block soon increased, and now *exercise did not remove it.* After seven days of this medication the block was so marked that every second ventricular systole was missed (Fig. 6). A few days after the drug had been stopped the condition was as before its administration.

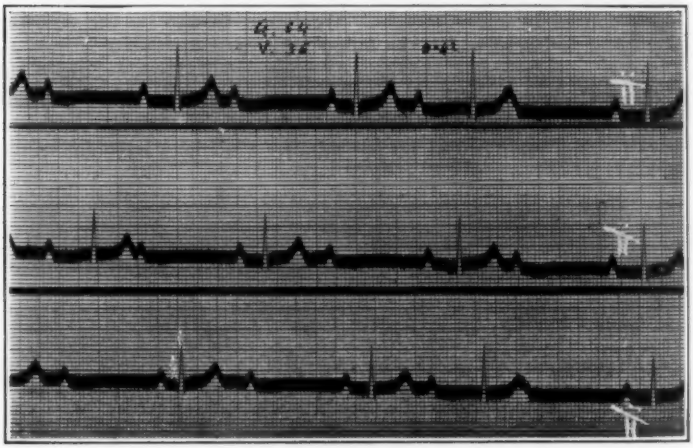

FIG. 6.—Increase of heart-block in same patient as Fig. 5 after a course of small doses of atropin.

It is evident that if atropin be given in the treatment of partial heart-block the dose must be large or the block will be increased rather than diminished.

In a few cases of Graves' disease, in which we tried small doses of atropin, there seemed to be some slowing of the heart-rate, but one would need to test this in a large series of patients before being sure of this. It is interesting to remember that it has long been the practice of many clinicians to give belladonna in this disease,

and our findings would tend to support scientifically what has always seemed to be a purely empirical treatment.

Our work has chiefly been done in cases of regular heart, but, with the collaboration of Dr. Jamieson and Dr. Hepburn, we tried the effects of small doses of atropin in some cases of auricular fibrillation, some under the influence of digitalis and others without this. The ventricular rate was never lessened and usually hastened. This apparently paradoxical result can probably be explained as follows: Sir Thomas Lewis[7] has shown that, while large doses of atropin by paralyzing the vagi cause increase in the refractory period, and in the duration of circuit movement with consequent lessening of auricular oscillations and often of ventricular systoles, stimulation of the vagi cause the opposite effect, with consequent hastening of the auricles and ventricles. Now, atropin in small doses stimulates the vagi, and hence may hasten the heart in the abnormal condition of auricular fibrillation. Hence, here it would be useless to use atropin as an adjuvant to digitalis. But it is otherwise in regular hearts and we have in atropin in small doses a drug that will slow such and which will enhance the effects of digitalis in such cases.

Summary. Atropin has two distinct effects upon the heart-rate when this is regular. In small doses it merely slows it, probably by stimulation of the vagal centers. In large doses, of course, it hastens it by paralyzing the vagal endings in the heart. It also then tends to remove any existing heart-block. If the dose be neither large nor small there will be no change in the heart-rate, the two effects of stimulation of the vagal centers and partial paralysis of the nerve-endings neutralizing each other. As already mentioned, individuals vary very much in their reaction to atropin. In most adults $\frac{1}{100}$ grain will merely slow the heart, in some no effect will occur while in a few a slight hastening sets in. In the last two groups it is usually only necessary to lessen the dose to get the slowing effect.

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THE MYOCARDIUM IN NON-INFECTIOUS MYOCARDIAL FAILURE.*

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When symptoms of chronic myocardial failure are present many clinicians make a diagnosis of chronic myocarditis, without regard to the pathological type of heart disease that may be present. Others use the term chronic myocarditis in a narrower sense to include only idiopathic hypertrophy with myocardial failure (hyperpiesia).

In chronic myocardial failure patches of fibrous tissue of varying distribution and size are frequently found in the myocardium and, according to one view, these are inflammatory in origin. Aschoff and Tawara[1] and Coombs[2] consider that some fibrosis may result from acute rheumatic fever. Brooks[3] finds fibrosis in a high percentage of cases of endocarditis. According to another view, the fibrosis for the most part is not infectious in origin and, to express the idea, such terms are used as senile heart, the arteriosclerotic heart, cardiosclerosis, etc.

The purpose of this paper is to determine the extent and character of the anatomical changes in the myocardium in chronic myocardial failure and to find the cause of these changes.

Material. A detailed gross and microscopical study was made of the myocardium in 102 hearts which had been preserved and were available for study. The coronaries were carefully traced to determine the extent of the thickening of their walls and the narrowing of their lumina. The degree of coronary sclerosis is expressed in grades of 1 to 4. A grade 1 signifies just enough thickening to be noticed, and grade 4 signifies a condition where the coronaries are practically closed in one or more places. Degrees 2 and 3 are intermediate. Degrees 1 and 2 are referred to as slight and 3 and 4 as serious. The condition of the orifices was especially noted. This is particularly important in cases with syphilitic aortitis. The orifices are never seriously involved in arteriosclerosis of the senile type. Both gross and microscopical search was made for thrombi in the coronaries in various parts of the heart wall. The myocardium of both right and left ventricles was dissected for the gross determination of fibrotic areas. Microscopical sections were studied from five different areas: From both apices, from the middle part of both ventricles and from the septum. A careful

* The term non-infectious includes conditions not immediately associated with an acute infectious or toxic process.

search was made for fibrotic areas and inflammatory processes, such as exudates and Aschoff nodules.

Conditions in which Non-infectious Myocardial Failure May Occur. For convenience the 102 cases of myocardial failure have been separated as follows: Group I, cases of hyperpiesia that died of myocardial failure, 37 cases. Group II, cases of hyperpiesia with slight cardiac decompensation that died of cerebral hemorrhage, 7 cases. Group III, cases of chronic glomerulonephritis with cardiac decompensation, 3 cases. (Twenty other cases of chronic glomerulonephritis without cardiac failure, not included in the series of 102 hearts, have also been studied for comparative purposes in respect to the presence of myocardial fibrosis.) Group IV, cases of myocardial failure with right ventricular hypertrophy and dilatation resulting from increased intrapulmonary resistance, 4 cases. Group V, cases of sudden death associated with coronary sclerosis without previous symptoms of cardiac decompensation, 19 cases; in 6 of these thrombi were found in the coronaries; from the size of the hearts it is evident that a hypertension had been present in all of these except 3. (Groups I to V inclusive may be considered for the most part hypertensive hearts.) Group VI, hearts with hypertrophy from healed valvular defects, 21 cases. Group VII, hearts with luetic aortitis with involvement of the aortic ring (aortic insufficiency), 9 cases. Group VIII, cases with cardiac failure following hypertrophy due to an adherent pericardium, 2 cases.

Frequency. Non-infectious myocardial failure occurred 202 times (12 per cent) in a series of 1682 adult necropsies performed at the University of Minnesota during the years 1920–1923. Approximately two-thirds of these 202 hearts are hypertensive (hyperpiesia, glomerulonephritis and right ventricular hypertrophy) types. The remainder are cases of valvular defects, syphilitic aortic insufficiency and adherent pericardium.

Structural Changes in the Myocardium. The anatomical conditions which may be considered as causes of myocardial failure are: (1) Coronary sclerosis; (2) an inflammatory process; (3) fibrosis (atrophy of the fibers with replacement by connective tissue).

Coronary sclerosis was found in minor degrees in 44, and in serious degrees in 23 of the 102 hearts (Table I). Of the 23 with serious coronary disease 6 were in Group I, 1 in Group II and 19 in Group V. Severe coronary sclerosis occurs only in these three groups. Minor degrees of coronary sclerosis are common in advanced life and seem to be independent of other diseases. In 35 hearts the coronary arteries were normal.

Evidences of a slight degree of *chronic inflammation* are present in 10 of the 102 hearts—in 1 with right ventricular hypertrophy, in 7 with valvular defects, in 1 with syphilitic aortitis and in 1 with adherent pericardium (Table II).

In 50 of the 102 hearts no *myocardial fibrosis* was found (Table

TABLE I.—CORONARY SCLEROSIS.

Group.	No. of cases.	Grades.				Absent.	Present.
		1.	2.	3.	4.		
I	37	19	6	5	1	6	31
II	7	1	2	0	1	3	4
III	3	0	0	0	0	3	0
IV	4	0	0	0	0	4	0
V	19	0	0	13	6	0	19
VI	21	7	3	0	0	11	10
VII	9	2	0	0	0	7	2
VIII	2	1	0	0	0	1	1
Total	102	30	14	15	8	35	67

TABLE II.—EVIDENCES OF CHRONIC INFLAMMATION.

Group.	No. of cases.	Chronic myocarditis.			Aschoff nodules.			Absent.	Present.
		R.–L.	R.	L.	R.–L.	R.	L.		
I	37	0	0	0	0	0	0	37	0
II	7	0	0	0	0	0	0	7	0
III	3	0	0	0	0	0	0	3	0
IV	4	1	0	0	0	1	0	3	1
V	19	0	0	0	0	0	0	19	0
VI	21	1	1	1	1	2	4	14	7
VII	9	1	0	0	0	0	0	8	1
VIII	2	0	0	0	0	0	1	0	1

TABLE III.—MYOCARDIAL FIBROSIS.

Group.	No. of cases.	Gross fibrosis.			Microscopical fibrosis.			Marked.	Moderate.	Slight.	Absent.	Present.
		R.–L.	R.	L.	R.–L.	R.	L.					
I	37	0	0	11	14	0	6	1	6	13	17	20
II	7	0	0	0	0	0	2	1	1	0	5	2
III	3	0	0	0	0	0	0	0	0	0	3	0
IV	4	0	0	0	1	0	0	0	0	1	3	1
V	19	0	0	10	13	0	4	5	7	5	2	17
VI	21	0	0	5	7	0	0	0	0	7	14	7
VII	9	0	0	0	3	0	0	0	0	3	6	3
VIII	2	0	0	1	2	0	0	0	0	2	0	2
Total	102	0	0	27	40	0	12	7	14	31	50	52

III). In 31 it was present in only a slight degree and therefore cannot be considered as a cause of myocardial failure. In the 21 remaining hearts fibrosis was present in moderate or severe degrees, and may have contributed to the failure of the muscle. These 21 cases are all in Groups I, II and V, in hearts in which coronary sclerosis is conspicuous.

Relation of Myocardial Fibrosis to Coronary Sclerosis (Tables I and III). In the 37 hearts of Group I myocardial fibrosis was found in 20, in 19 in association with coronary sclerosis and in 1 in the absence of coronary disease. The distribution of the areas of fibrosis corresponds to that of the diseased arteries. All hearts with serious coronary sclerosis show some myocardial fibrosis.

In the 7 cases of Group II coronary sclerosis was found in 4 hearts, in 2 of which myocardial fibrosis also occurred.

In the hearts of Group III there is neither coronary sclerosis nor myocardial fibrosis.

In Group IV, with right ventricular hypertrophy, no coronary sclerosis is found. Myocardial fibrosis is present in 1. This heart is from a girl, aged eighteen years. The degree of fibrosis is slight, and Aschoff nodules are found. In this case the fibrosis is evidently rheumatic in origin.

In the 19 hearts in Group V coronary sclerosis occurs in all, and myocardial fibrosis is present in 17. In all of the hearts coronary sclerosis is of a severe degree, and the amount of myocardial fibrosis is usually correspondingly extensive.

Minor degrees of coronary sclerosis were found in 10 in the 21 hearts of Group VI, in which failure was due to healed defective valves. Myocardial fibrosis is present in a slight degree in 7 of these 21 hearts. It occurs only in 1 where there is no coronary sclerosis. In this group coronary sclerosis, although of slight degree, may be a factor in causing myocardial fibrosis, but there is another more probable cause, since Aschoff nodules are present in 7, indicating a previous rheumatic infection, which may also give rise to slight fibrosis.

In the 9 hearts of Group VII, in which myocardial failure followed syphilitic aortitis, coronary sclerosis is present in 2, and in both of these cases myocardial fibrosis is present to a slight extent. In 1 the fibrosis is associated with a chronic inflammation, probably syphilitic in origin. In the other the fibrosis probably followed coronary sclerosis.

One of the 2 hypertrophied hearts with adherent pericardium shows slight coronary sclerosis. Both show myocardial fibrosis, but in the one with the normal coronaries Aschoff nodules are present.

The relation of myocardial fibrosis to coronary sclerosis is obvious, especially in Groups I, II and V, in which there has not been a previous infectious process. It appears highly probable that coronary sclerosis causes all myocardial fibrosis, except a few of slight

extent due to rheumatic infection and rare instances of myocardial lues.

Relation of Myocardial Fibrosis to Rheumatic Infections (Table II). That a fibrosis of the myocardium, periarterial in character, may follow rheumatic infections has been shown by Beattie and Dickson[4] and others. The presence of Aschoff nodules as an indication of a rheumatic infection has been established. These tend to disappear after an acute attack, but they may remain for years. It is generally believed that rheumatic infections are responsible for about 85 to 90 per cent of healed valvular defects, and that in practically all cases of valvulitis there is a myocardial involvement.

In none of the hypertensive hearts is there any indication of a rheumatic myocardial involvement, shown by the presence of the Aschoff nodules, except in 1. This is the heart of a girl, aged eighteen years, which failed from increased intrapulmonary resistance. Neither is there any indication of a previous rheumatic infection in the 9 hearts with aortic insufficiency associated with syphilitic aortitis. In the 7 cases with valvular defects in which myocardial fibrosis is present it is probably due to a rheumatic infection, since the Aschoff nodules are found. The fact that a non-tuberculous pericarditis is frequently rheumatic in origin would suggest that the fibrosis found in the hearts with an adherent pericardium was produced by a rheumatic infection.

It is seen that there is evidence of a rheumatic origin of myocardial fibrosis in only 10 of the 52 cases. In general, it may be said that rheumatic fibrosis is always of slight degree, and that in most instances myocardial fibrosis is not rheumatic in origin. As far as these observations go, an extensive myocardial fibrosis is never rheumatic.

Relation of Myocardial Fibrosis to Lues (Table III). Warthin[5] is apparently of the opinion that myocardial fibrosis is usually due to syphilis. He states that the fibroid heart is the ultimate outcome of all latent syphilis. In his material he found that coronary sclerosis might or might not be associated with syphilitic myocarditis. He found marked coronary sclerosis to be a rather rare association. Even in the 9 cases of definite syphilitic aortitis in our series there were only 3 instances of myocardial fibrosis, and 2 of these seemed to be due to coronary sclerosis of the ordinary type. Lues of the myocardium appears to be rare.

Relation of Myocardial Fibrosis to Strain. The various kinds of strain which may result in hypertrophy and dilatation of the heart are: (1) Increased systemic arterial resistance, as in essential hypertension and chronic glomerulonephritis; (2) increased pulmonary resistance, as is found in bronchial asthma and pulmonary emphysema; (3) strain, non-hypertensive in character, as that found with valvular defects, syphilitic aortic insufficiency and adherent pericardium.

In the hyperpiesia hearts (Groups I and II) myocardial fibrosis occurs in 14 in both ventricles and in 8 in the left ventricle alone. It is true that there is strain on the right ventricle after decompensation begins, but the chief strain is on the left ventricle, and one would expect much more pronounced changes on the left side if hypertensive strain causes fibrosis. The 22 hearts without fibrosis in Groups I and II average 565 gm. in weight. Judged by their weight these hearts were subjected to as high a degree of hypertension as those with fibrosis.

In the 3 cases of chronic glomerulonephritis with myocardial failure there was no fibrosis. In 20 other cases of chronic glomerulonephritis, with hearts ranging in weight from 500 to 760 gm., there was no fibrosis except in 1, aged sixty-nine years, with coronary sclerosis. The persons with chronic glomerulonephritis are in general much younger than those with myocardial fibrosis.

There is no fibrosis in the cases of right ventricular hypertrophy, except in 1 which had associated Aschoff nodules.

It is apparent therefore that there is no evidence to support the view that hypertensive strain causes myocardial fibrosis. Fibrosis is absent in cases of hypertension that do not have coronary sclerosis. This agrees with Allbutt's[6] statement that in hyperpiesia hearts the myocardium is usually normal microscopically.

Judged by the extent of the ventricular hypertrophy there is often a severe strain on the myocardium in hearts with valvular defects. If such strain is a cause of myocardial fibrosis, as believed by Stadler,[7] these hearts should show this change. In the 21 hearts with valvular defects myocardial fibrosis of a slight degree was found in 7, and in all of these Aschoff nodules were found, indicating that the fibrosis was inflammatory in origin. In the 14 cases without fibrosis the average weight was 550 gm., indicating long-continued myocardial strain. In 1 case, a man, aged forty-four years, with aortic stenosis, the heart weighed 1130 gm., but no fibrosis was found.

In the 9 cases of luetic aortic insufficiency a slight fibrosis was found on microscopical examination in 3. In 1 of these there were many lymphocytes and the appearance suggested lues. There is often some narrowing of the coronary orifices in this disease. There is no evidence here that strain causes fibrosis.

In 1 of the cases of adherent pericardium the slight myocardial fibrosis may be explained on a rheumatic basis, in the other with a gross fibrosis the cause is not clear. It may be due to coronary disease or to a rheumatic infection.

There is no satisfactory evidence that strain of the non-hypertensive type ever causes myocardial fibrosis.

Conclusions. The anatomical changes in the myocardium have been studied in myocardial failure resulting from hyperpiesia,

chronic glomerulonephritis, right ventricular hypertrophy, defective valves, luetic aortitis and adherent pericardium.

There are no anatomical changes except coronary sclerosis and myocardial fibrosis.

Coronary sclerosis of serious degree was present in 22.5 per cent.

Myocardial fibrosis was found in a marked or moderate degree in 20.5 per cent and in a slight degree in 30 per cent.

There is usually a close correspondence between the situation and extent of myocardial fibrosis and the distribution and degree of the coronary sclerosis.

Myocardial fibrosis is usually due to coronary disease, but occasionally rheumatic infections may give rise to a slight degree of fibrosis.

Myocardial strain (hypertensive or non-hypertensive) is not a cause of myocardial fibrosis.

Luetic myocarditis is rare.

Myocardial failure is rarely due to anatomical changes in the myocardium. It may be explained as an exhaustion of the cardiac muscle.

True chronic inflammation of the myocardium is very rare. What is commonly called "chronic myocarditis" is usually myocardial fatigue resulting from the various conditions mentioned above.

Approximately half of the cases of myocardial failure show no anatomical changes in the heart muscle.

The anatomical changes in the heart muscle are seldom sufficient in themselves to cause death.

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A STUDY OF FOUR THOUSAND REPORTED CASES OF ANEURYSM OF THE THORACIC AORTA.

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The fact that there are over 5000 cases of thoracic aneurysm reported in the literature shows the subject is regarded as one of importance and interest. A majority of the papers consist of case

reports with a comment upon some unexpected feature, not rarely an unforeseen postmortem diagnosis. It was thought advisable to undertake a review of the subject in order to ascertain, if possible, the reasons for continuing to make mistakes and to suggest remedies. In this paper, no statistical report previously made will be included unless the report was based upon personal observation. No theories will be advanced to explain the numerical results of the survey since the aim of the report is to make a statement of fact rather than engage in the polemical aspects of the problem.

Incidence. Thoracic aneurysm is not rare. It probably represents the cause of mortality in 0.1 to 0.5 per cent of deaths in American cities. In postmortem statistics, it is found in a variety of figures varying from 0.1 to 0.9 per cent; 0.3 per cent being about the average. More instructive is the relationship between the reports of: (1) Out-patient dispensary services and (2) hospital in cases. The diagnosis is made nearly fifteen times as often in the latter group. This disparity cannot be accounted for upon the basis of a difference in the degree of symptoms except in the minority of cases. It can be explained by assuming a difference in the degree of minuteness of the examination given in the two services.

Predisposing Causes. SEX. Aneurysm of the thoracic aorta is 5.6 times as common in males as in females. All statistics give males a marked predominance although the figures vary from 10 to 3 up to 11 to 1.

CHART I.

AGE. Aneurysm may be seen at any age. It has been reported in the infant and in the very aged. The curve of incidence rises slowly from birth and reaches a maximum in the period from thirty-six to forty years and then falls more slowly. While aneurysm is usually discovered in the years of greatest physical activity, it must be considered as a diagnostic possibility at any age. In 3690 cases, the exact age was stated and 2791 or about 75 per cent were between the ages of thirty and sixty.

AGE INCIDENCE IN MALES. The curve of incidence in males rises slowly from birth until the twenty-fifth year and then rapidly reaches a maximum in the thirty-six to forty-year period. The curve of descent is more gradual. The course of the curve confirms the universally accepted dictum that the maximum frequency of aneurysm corresponds to the period of greatest incidence of syphilitic vascular disease.

AGE INCIDENCE IN FEMALES. The largest number of cases in females is found in the forty-six to fifty-year period, ten years later

than the maximum for males. Up to the forty-one to forty-five-year period, the curves are similar but in the next five years instead

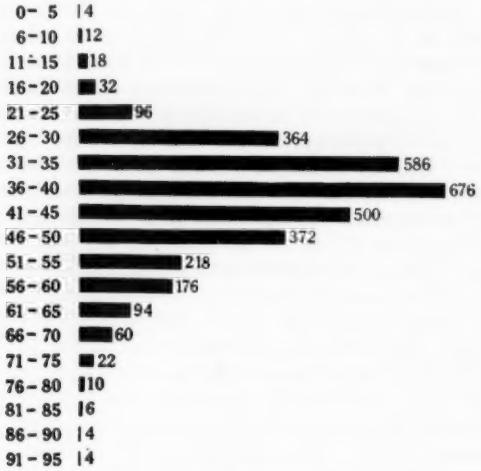

CHART II.

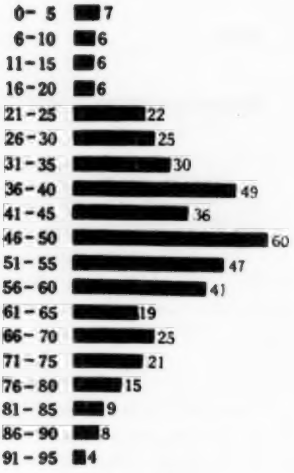

CHART III.

of the expected fall, there is a rise. From this age until sixty-five there is a steady fall and then the third apex. At seventy-five, the number of cases for both sexes is equal. Owing to the fact that, in

only 436 female cases the exact age was stated, it is inadvisable to draw conclusions as to the significance of the various peaks. The first two apices seem to correspond to the two ages of syphilitic infection. The third is not solely arteriosclerotic since there is no similar apex in the male.

Race and Occupation. The colored race is notoriously liable to aneurysm probably due to the increased incidence of syphilis in that race. The role of occupation has been stressed by many writers. Sudden violent exertion in adults precipitates many latent aneurysms but probably does not cause them. The writer recently observed a syphilitic male, aged thirty-four years, who was under treatment for syphilitic aortitis. His occupation of a truck driver necessitated heavy manual labor. Sometime ago while cranking a machine, the engine back fired, the crank striking the man in the chest. Since that time, the man has complained of the symptoms and has given the physical signs of aneurysm of the ascending aorta. Had not the writer had knowledge of the patients' syphilitic aortitis, he might have been inclined, as many others have been, that the etiology was strain or trauma. It is probable that the association of syphilis, alcohol and hard work in the same type of individual is more important than occupation itself, although there has been a sufficient number of aneurysms found in non-syphilitic children (usually suffering from whooping-cough) to warrant the view that stress and strain play more than a minor part in some cases.

Determining Causes. Infection. A very great majority of the cases are due to infection, syphilis standing out beyond any other. Estimates vary from 25 per cent (Klemoerer) up to 92 per cent (Rasch). Instead of citing proof of this point from the pathological standpoint, it was thought more interesting to note the time interval between the infection and the production of the first symptoms of aneurysm. This was noted in 200 cases and it was found that the average time was twenty years, which corresponds in general to the upper limit of the maximum of time interval for syphilitic aortitis. The minimum time was one year (syphilitic aortitis has been reported within six months). The upper limit was fifty-six years after infection. In 1 case a beginning aneurysm was found at autopsy when the chancre was still upon the penis. The possibility of coincidence is too great to include this case. The importance of these figures outside of showing the usual time interval is to emphasize that the syphilitic individual remains throughout his life potentially aneurysmal. Of the other infections, the septicemias are at times the cause of mycotic embolic aneurysms, while other infections may pave the way for an arteriosclerotic process.

Hypertension. Prolonged hypertension plays a part in the production of arterial degeneration. Much more important in the production of aneurysm is sudden increased intravascular tension resulting from sudden violent physical exertion.

Location of the Lesion. The ratio of aneurysms in the various portions of the aorta is approximately 10–7–3–1. This has an important relationship to the symptoms.

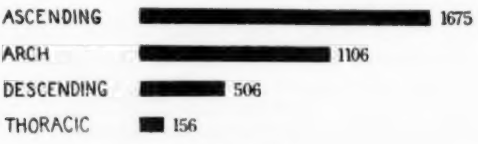

CHART IV.

1. ANEURYSM OF THE ASCENDING AORTA. Aneurysm of the ascending aorta has been divided into two types: (1) Of the intrapericardial portion (aneurysm of symptoms) and (2) of the extra pericardial portion (aneurysm of physical signs). In reference to the first type, it should be noted that they are usually found at the sinus of Valsalva upon the right anterior surface of the aorta. These aneurysms of symptoms are prone to rupture before manifesting marked physical signs unless aortic regurgitation complicates. The symptoms are those of syphilitic aortitis. Since the second type has large sacs which displace and compress neighboring structures, they have been denominated "the aneurysm of physical signs."

2. ANEURYSM OF THE ARCH. This is another aneurysm of symptoms. They are usually found upon the posterior or posterior inferior part of the vessel and tend to involve the orifice of the innominate artery. The usual growth is backward so that the various vital structures in the vicinity of the dorsal surface suffer early. Anterior growth causing midline tumor is known but is not as common.

3. ANEURYSM OF THE UPPER DESCENDING AORTA. This is an "aneurysm of latency." In spite of the many possibilities for the production of respiratory, esophageal, or vertebral symptoms, this type is especially liable to be overlooked. The frequency of failure to discover aneurysm of this nature is due to the fact that the findings are frequently to be discovered upon the back, the examination of which is usually minimized. Anterior growth in the left subclavicular space is known. It should be emphasized that the location of the sac in the various forms is not pathognomic but only suggestive.

4. ANEURYSM OF THE LOWER DESCENDING AORTA (THORACIC). This is another aneurysm of latency differing from the above in merely the greater liability to pleural or lung rupture and a rarity to esophageal rupture. The fourth class does not merit distinction from the aneurysm of the upper descending aorta but it was thought advisable to retain the conventional terminology.

Symptomatology of Aneurysm of the Aorta. PAIN. In 1011 cases the symptomatology was noted. Pain was the first and chief complaint in 29 per cent. It was regarded as located in the chest in 18 per cent, left shoulder 4 per cent, right shoulder 3 per cent and in the back 4 per cent. For these reasons, the location of the pain should not be considered diagnostic. Since the pain may be felt in a variety of locations, any obscure pain in this region should excite a suspicion of aneurysm. In the absence of pulsation or swelling, pain in the precordia is often diagnosed as angina pectoris. Pain in either shoulder or back is often designated by the confusing and meaningless term "rheumatism." The importance of this is realized at once when we see rheumatism heading the list of wrong diagnoses. Pain in the intercostal spaces is often labeled neuralgia whereby a symptom is confused with a disease.

TYPES OF PAIN. For the purpose of clarity, the pain will be described as manifesting itself in one of three forms.

(*a*) *Anginoid.* This is apt to occur early in the disease. In the majority of cases, the anginoid pain is associated with aneurysm of the sinuses of Valsalva or the ascending aorta. Opinions as to the cause of the pain vary. From the different schools may be cited the following: (1) Involvement of the nerve plexus in the wall of the aorta; (2) stretching of the aorta; (3) pressure upon the coronary arteries. Like angina pectoris, it is often radiated down the arm and associated with numbness or tingling in the fingers. Exertion is especially apt to provoke an attack. The great importance of remembering this expression of aneurysm is seen when we recall that it is practically indistinguishable from pain of simple syphilitic aortitis or non-syphilitic angina pectoris. By this last phrase, the writer endeavors to include all of the diverse forms of disease which may present pain in the region of the heart. It makes an appearance at a time when other symptoms are apt to be absent and if disregarded and misinterpreted spells consternation for the unwary physician. Aneurysms associated with pain of this nature are prone to rupture by sudden physical exertion without further warning so that muscular effort must be curtailed.

(*b*) *Pressure Pain.* The typical pain of aneurysm is not present until the growth reaches the chest wall. It therefore comes late in the life history of aneurysm. Eroding pain is best seen in the descending and thoracic types which are often latent until late in the course. Many writers have noted that pain due to erosion of the ribs and sternum is much less marked than erosion of the vertebra. It is still more remarkable and not rare to see very decided erosion occurring without any pain at all. In addition to erosion, "pressure pain" may be seen when there is involvement of nerve trunks. This is particularly liable to be "neuralgiac" in character and often aneurysms of the descending aorta may present themselves under disguise of an intractable neuralgia. Finally, there may be pressure

pain when there is pressure upon any structure in the thorax so the old axiom that any pain not corresponding to definite disease of the thorax should excite a suspicion of aneurysm, has much truth in it.

(*c*) The third type of pain is difficult to name and occurs in dissecting aneurysms. It is a sudden terrific pain in the chest, usually associated "with collapse from which the patient may or may not rally." Radiation into the chest, abdomen, back, or shoulders is common while no report of an instance in which the pain passed into the arms can be found. When cases live for more than a few minutes, they present usually the clinical picture of a severe angina pectoris and in a short time (hours or days), they have a second attack and death. In exceptional instances, death has been delayed and case reports are not unknown which describe an attempt at an endothelial lining of the dissected channel. Many cases of double aorta are in reality this type of aneurysm.

Dyspnea. This symptom is seen in a variety of degrees and types. It is the most common symptom of aneurysm, being the first or chief complaint in 31 per cent of the cases. It is placed second here because in its milder forms it is apt to be disregarded by the patient and elicited only upon inquiry. In its mildest and most common form, it consists of a mere substernal oppression, is increased upon exertion and indistinguishable from syphilitic aortitis. More severe is the form due to pressure upon the trachea and large bronchi expressed as dyspnea steadily increasing in severity. Either of the above are exceedingly liable to be diagnosed "failing heart" (in fact, part of the symptoms are due to circulatory disturbances in the lungs, either from the impaired valves or from passive congestion due to pressure upon the bloodvessels). There is a paroxysmal type of dyspnea which is very important. These attacks may be occasioned by changes in posture and the patient often assumes unusual positions in order to avoid their production (pain may also be relieved by posture). The cause is not known, some attributing the symptom to pressure upon the vagus, others the recurrent laryngeal, but whatever its ultimate etiology it is rarely seen unless there is actual pressure upon the trachea or large bronchi. The fact that asthma is third in the list of wrong diagnoses emphasizes the great importance of this symptom.

Cough. This is the third great symptom of aneurysm, being the first symptom or chief complaint in 19 per cent of the cases. Like other symptoms it varies in degree and type. The commonest form is seen in association with "attacks of colds." A very frequent history is that the patient has in the last few years been having attacks of colds, the last one of which has persisted or is becoming worse. This is found as the first symptom in 10 per cent of the cases. These are frequently diagnosed as chronic bronchitis or winter cough (?). Brassy, gander cough is present and quite characteristic in only a minority of the cases. As a rule, it is present when there

is involvement of the recurrent laryngeal nerve which practically restricts it to arch aneurysms. Since the symptom occurs in only a minority of instances while its presence is suggestive, its absence means but little.

Sputum. This can be considered along with cough. Usually when gander cough is present, there is little or no sputum. When arch or descending aneurysms press upon the left bronchus, an exceedingly common occurrence, a large amount of sputum may be noted. The resultant bronchorrhea is in most instances associated with some bronchiectasis or low-grade infection in the area beyond the obstruction. When sputum is present, it is modified in about one-fourth of the cases by the addition of blood (chief complaint in 2.9 per cent). This bleeding may be of three types: (1) A large hemorrhage due to ulceration through the left bronchus or less commonly the trachea which is fatal in a few minutes; (2) a group in which profuse hemorrhages are seen over a period of months due to leaking of the aneurysm and subsequent blocking of the rent by means of a clot; (3) those cases which have a low-grade tracheobronchitis, a passive congestion from a failing myocardium, pressure, pulmonary infraction, or actual rupture into the lung substance. The last two are relatively unimportant since they occur just before death. The association of cough with loss of weight, hemoptysis, and fever makes tuberculosis second in the list of wrong diagnoses.

Tumor. This is at times the chief complaint and may be one of the early symptoms, especially in arch tumors growing forward. As a rule, it is overemphasized as a symptom since at the time it appears diagnosis can be made by a tyro. The process may be painless but unfortunately for the sufferer this is quite unusual. As a rule, tumor is not an early symptom and in many cases may be absent throughout the entire course of the disease. When the pulsating tumor has appeared, a diagnosis is rarely in doubt because at this late stage most of the other symptoms or signs will be well marked. Pulsating empyema has caused confusion in a few instances.

Dysphonia. A common symptom in arch aneurysm is dysphonia, but is a chief complaint only one-sixth as frequently as pain. The voice may assume any character, usually husky or hoarse although it may be "cracked, tremulous, or even aphonia" may be present. Dysphonia is important as a symptom because it is indicative of the location of the lesion and not because of its extreme frequency. It rarely causes diagnostic difficulty because this symptom is rather well understood. In a few cases the diagnosis was tuberculous laryngitis or chronic laryngitis. The symptom was absent in one-fourth the cases in which it was mentioned. Cord changes antedate voice abnormalities.

Dysphagia. This symptom is closely allied to dysphonia. In arch aneurysms it is produced by pressure through the bifurcation of the trachea. The lower the aneurysm is upon the descending

aorta, the less frequent is dysphagia. As a chief complaint it is not common, being found in only one-half as many cases as dysphonia. Dysphagia was absent in 46 per cent of the cases in which it was mentioned which is somewhat surprising since rupture into this structure is third in frequency.

Loss of Weight and Appetite. The first is much more common than the second. Loss of weight is the chief complaint in 1.9 per cent while loss of appetite is the chief complaint in 0.5 per cent. As would be expected, these symptoms are present only in those cases which have lasted over a period of time. Loss of weight may be due to a number of causes. Among them are: (1) Pain anywhere in the thorax; (2) pain on swallowing, and more rarely (3) pressure upon the thoracic duct. Loss of appetite while uncommon may be a prominent feature in some cases.

Palpitation. Among the common symptoms will be found palpitation, ranking at about the same level as dysphonia as a chief complaint. Unfortunately it has no peculiar feature which seems to differentiate it from other types of palpitation.

Fever. This is not really a symptom but a complication. It must be emphasized as important since with bronchostenosis and subsequent bronchiectasis, low-grade infection is not at all rare. "Chronic pneumonias" are a frequent cause of death. Other symptoms of less importance are, disturbances of sweating, herpes, hiccough.

Pulsation. Among the most important objective phenomena is found pulsation. Although rarely a chief complaint, it is more common than tumor as a finding. The first type of pulsation is the diffuse general shock that may be seen anywhere in the chest. It is particularly frequent in ascending aneurysms complicated by cardiac hypertrophy due to a concomitant aortic regurgitation. Cases having a large mouth to the aneurysm may have pulsation over the sac. The second type of aneurysmal pulsation is diffuse. It differs from the preceding in that no distinct shock is noted. Pulsations are most frequently noted in the second right or left intercostal spaces or in the back. With the exception of the last, pulsation is not in any way characteristic of aneurysm. Broadbent's sign may give rise to confusion but is not a pulsation but a tug. Pulsation in the back should be emphasized since this group of cases often have but a few other symptoms. Expansile pulsation is often noted late in the development of the aneurysm, but is a tactile rather than visual impression.

Cyanosis. In ascending aneurysms there is great opportunity for pressure upon the superior vena cava, the pulmonary artery or the right auricle, while in arch tumors, there is the same liability to pressure upon the innominate vein, the subclavians or the jugulars. In the descending form, the azygos system may be involved. In reference to the superior vena cava, it is surprising how nearly

complete obliteration may be found without marked symptoms. Should rupture occur into either vena cava, the pulmonary area or right heart, cyanosis may be a marked finding. Pressure upon the other vessels mentioned causes cyanosis in the areas which they drain. Closely allied to cyanosis is visible enlargement of the veins. Peculiar pictures may present themselves; as unilateral cyanosis of the head and neck (jugular compression) involving one arm (subclavian compression) or the head, neck, and arms (innomiate or superior vena cava compression). In some cases we find the intercostal mammary group of veins enlarged (compression above the azygos major) or again the anterior chest wall may show a dilated plexus of veins and edema of even the posterior thoracic wall (deep cervical intercostal communication). Compression of the azygos major is not rarely a cause of right sided pleural effusion which not only adds to the patients' discomfort but helps to obscure the diagnosis. Inferior vena cava compression is not common.

Ocular Phenomena. Ocular symptoms although well known should be mentioned because of their frequent absence. They are absent in over one-half of the cases in which they are mentioned as a symptom. Aneurysms irritating the superior cervical sympathetic may show dilated pupils, widened slit, protrusion of the bulb, or in the stage of paralysis may be seen miosis, exophthalmos and sympathetic ptosis. Changes in the size of the pupils may be caused by vascular conditions. More important than dilatation or contraction is a variance in size in the two. Separate and distinct from the vascular disease, pupillary findings due to the concomitant luetic involvement of the central nervous system may be present. As in the case of other symptoms, positive findings are suggestive while negative findings should occasion no wonder.

Involvement of the Recurrent Laryngeal. This sign is frequently overlooked because of, either the inability to make the examination or, more commonly, neglect. It might be expected from the location of the laryngeal nerves that arch aneurysms might produce changes in their function. When involved, it is usually the left that is disturbed, more rarely the right and still more unusual is involvement of both. As a rule the cord may be paralyzed a considerable length of time before there is any voice change. Later when the cord passes back into the "cadaveric" position the various types of dysphonia appear. It is therefore important to examine all the vocal cords of aneurysm without waiting for voice changes since cord changes as a rule precede and outnumber in frequency voice changes.

Physical Signs. Palpation. All the above symptoms and signs belong properly under inspection with the exception of expansile pulsation. Among the other very important findings of palpation are those variations found in the pulse. From a theoretical standpoint the pulse in the aneurysmal sac should be later than the apex

impulse but since the time interval is so short this sign gives practically little information. Palpation of the various arteries may give some information but since palpation is usually confined to the radial artery, aid from this method is unusual. In case reports, observation of the pulse is mentioned about as often as the pupils but the first more frequently shows abnormality. Inequality of the radial pulses in aneurysm has long been known but as a matter of fact this examination is rarely done unless other signs of aneurysm are manifest. As a rule the pulse is smaller upon the side of the aneurysm. While testing for inequality of the two pulses not rarely will be noticed what appears to be a delay of one of them. The delay is usually found in the smaller pulse. Many types of tracings have been devised for the radical pulse but since a tracing of a single pulse gives nothing more than simple palpation this mode of examination might easily be omitted. Simultaneous tracings of the two radials is desirable when the exact location of the aneurysm is necessary, as for operative purposes. As might be expected from the above description of the pulse, variation is dependent partly upon the size of the sac and even more upon the character of its contents. A sac even though large, filled with a laminated clot, dampens the pulse but little.

Tracheal Tug. Ever since Oliver noted this phenomena the literature has had many reports upon this sign. The directions for eliciting it are too well known to need repeating. It is positive when the aneurysm presses upon the left bronchus or the trachea near the left bronchus and is most marked during inspiration. It is positive in much less than one-half the cases because of the anatomical requirements for its production. A few authors, especially Sewall, have pointed out that slight degrees of this phenomenon may occur in other conditions. For example in solid mediastinal neoplasms, in cases of tracheobronchial lymphadenopathy and it is not at all rare in pulmonary tuberculosis or left pleural involvement. Any condition anchoring the left bronchus to the aorta may produce this sign. Attention has been directed to the presence of this sign even in enteroptosis (Wenckebach). Briefly, it should be remembered that this symptom is absent in over one-half the cases and may be present in slight degree in other conditions.

Percussion. In percussion we have a most important finding, namely, dulness. In a majority of instances it is sub- or parasternal. As mentioned in the beginning of the review, aneurysms of the sinuses of Valsalva may never reach sufficient size to give rise to changes in dulness. However, ascending aneurysms with their large sacs will usually give rise to dulness to the right of the sternum. Arch aneurysms when not too deep will give rise to substernal or left parasternal dulness. However, mere dilatation of the aorta may give rise to this phenomena. In descending aneurysms the dulness may be found in the subclavian space, the axillary space or,

more commonly, in the left interscapular and left subscapular space. It is amazing how rarely posterior dulness is mentioned in case reports although nearly every text-book has emphasized it. Smith's tracheal percussion has never come into general use.

AUSCULTATION. The findings derived from auscultation are of two varieties: (1) The heart and aorta and (2) the lung. Examination of the heart may show the signs of aortic regurgitation, which often accompanies sinus aneurysms. As to the aneurysm proper there are several factors which make for variation in auscultatory findings. Adventitious sounds depend upon the contents of the sac and the conditions at the orifice. Among the positive findings one notes a dull first sound followed by a ringing accentuated second sound. Occasionally one hears a systolic "humming-top" murmur which is found in cases having a communication between the aneurysm and the superior vena cava, the pulmonary artery, or the various heart chambers. A bruit over an aneurysmal sac is not an important finding since it is absent in a great number of cases. Like many other findings its presence is additional evidence while its absence in no way influences the diagnosis.

In reference to the lungs are those findings associated with bronchiostenosis such as lagging respiration, diminished expansion, later, the findings of bronchiectasis, although as a rule these are not decided. Finally the signs of low-grade infection manifest themselves There may be merely a diminished respiratory murmur or in other instances the sound may be entirely absent. Findings of a pleural effusion or the pneumothorax may be superimposed upon the other lung signs.

Incorrect Diagnosis. Some of the reasons for making wrong diagnoses have been suggested. The incorrect diagnosis was noted in 130 cases.

Rheumatism	32	Failing heart	10
Tuberculosis	22	Mediastinal neoplasm	10
Asthma	18	Endocarditis	4
Chronic bronchitis	14	Angina pectoris	4

Pericarditis, pleurisy, carcinoma of stomach and esophagus, chronic laryngitis, tuberculous laryngitis, abscess of the lung, pleural effusion, and empyema each 2.

Duration of the Symptoms. In reference to this point, 830 cases were studied. These were not selected. The first large group consists of 312 cases, in which the duration was under three months. This figure is undoubtedly high since those cases in which death was the first symptom are much more apt to be reported than those which run a prolonged course. Of the aneurysms which run so short a course, there are two main types. The first are the aneurysms of the sinuses of Valsalva which are prone to early pericardial rupture. The second are the "early" deaths due to undetected descend-

ing aneurysms. It does not seem probable that the course of aneurysm is so dismal that one-third of the cases die in three months but more reasonable to suppose that statistics like those of Lemann, where death was not the first symptom and where more careful observation than the average reported case received, are more nearly correct for this first group.

0 to 3 months	312	5 to 6 years	14
4 to 12 "	234	6 to 7 "	6
1 to 2 years	128	7 to 8 "	6
3 to 3 "	70	8 to 9 "	6
3 to 4 "	22	9 to 10 "	4
4 to 5 "	8	10 to 20 "	18
		10 to 30 "	2

The roentgen-ray is diminishing the number of cases which are discovered for the first time in the postmortem room. In spite of the fact that a great majority of the cases die within a two-year period, it is better to look at the table from another angle. Just as we may expect to see aneurysm at any age, so must we expect it to last a variable time.

Death in Aneurysm. Death in cases of aneurysm may be due to one of three causes. The first consists of those cases which die of some disease separate and distinct from the aneurysm. This group needs no discussion. For convenience the remaining two causes may be described as those which die from rupture and those from the mechanical effects of the sac. About 52 per cent of the cases die from rupture.

TABLE I.—TABLE OF RUPTURES INTO THE VARIOUS ORGANS.

	No.	Per cent.		No.	Per cent.
Pericardium	369	31.0	Right lung	12	1.0
Left pleura	174	14.6	Right bronchus	12	1.0
Esophagus	112	9.4	Right ventricle	12	1.0
Right pleura	88	7.4	Left auricle	9	0.7
Left bronchus	85	7.1	Descending vena	8	0.6
Trachea	74	6.2	Left ventricle	5	0.4
Externally	61	5.1	Spinal column	4	0.3
Pulmonary artery	45	3.7	Hematoma thorax	4	0.3
Sup. vena cava	44	3.7	Stomach	3	0.2
Left lung	40	3.3	Both pleura	2	0.1
Mediastinum	20	1.6	Hematoma neck	1	0.8
Right auricle	13	1.0			
Total				1197	ruptures

Ruptures have certain interesting features. In the first place there is a high percentage of pericardial ruptures. These outnumber the instances of either left or right pleural rupture, but since they contain features in common, they may be discussed together. Ruptures into serous surfaces are extremely apt to occur without warning, and usually the tear is sufficiently large so that death occurs in a very short time (minutes or hours). As stated above the

rupture of this nature is extremely apt to occur at the time of sudden violent muscular effort, although reports were noted in which the case was found dead in bed or in a chair. Esophageal ruptures, like ruptures through other mucous membranes, are apt to be a slower process and frequently give repeated warning. Oozing over a considerable period of time is not uncommon and the diagnosis of carcinoma of the stomach or esophagus has been made in some cases. At the time of the hemorrhage or a profuse hemorrhage followed by a second after an interval of ten to twelve hours. Ruptures into the bronchi or the trachea are apt to be quite similar to esophageal. Occasionally there may be an immediately fatal hemorrhage but more commonly repeated slight hemorrhages or oozing

TABLE II.—TABLE OF RUPTURES INTO VARIOUS ORGANS.

	Asc. (365) per cent.	Arch. (226) per cent.	Desc. (125) per cent.	Thor. (50) per cent.
Pericardium	57.5	12.8	..	2
Left pleura	2.1	12.8	30.4	46
Esophagus	1.6	12.8	19.2	14
Right pleura	3.0	10.1	9.6	12
Left bronchus	0.2	13.7	23.0	4
Trachea	0.8	16.3	4.8	
Externally	4.9	3.8		
Pulmonary artery	10.1	1.3		
Sup. vena cava	8.4	1.7		
Left lung	0.5	3.5	4.8	10
Mediastinum	1.5	3.5	2.4	2
Right auricle	3.0			
Right lung	0.8	1.7	0.8	
Right bronchus	0.5			
Right ventricle	2.4			
Left auricle	0.2	0.8		
Left ventricle	0.8			
Spinal canal	..	..	1.6	4
Hematoma	..	0.4	0.8	
Stomach	..	0.4	..	4
Both pleura	0.2	0.4	0.8	2
Hematoma of neck	0.2			

over a period of time. Profuse bleedings with a long period of comparative freedom from hemorrhage is not rare. External rupture is probably more dramatic than those which have been described above. It must be emphasized that this is not a common termination of aneurysm. Usually the aneurysm points, not unlike an abscess (for which they have been lanced). Even when definite pointing has occurred, it is by no means assured that external rupture will occur. At times the aneurysm will "weep" externally for weeks and then end in rupture into some other structure. In rare instances the aneurysm ruptures into the subcutaneous tissues and subsequent gangrene occurs. Rupture into the pulmonary artery is one of the types in which a fatal issue may be delayed. When this occurs in addition to the signs of aneurysm, there is

sudden onset of cyanosis, orthopnea, the systolic "humming-top" murmur, or thrill. Edema of the upper extremities and head is by no means constant. Rupture into the superior vena cava has been well described by several authors and shows: Sudden onset with pain, dyspnea, some shock, feeble pulse with sweating, then cyanosis and swelling of the upper extremities, and a similar murmur and thrill as was mentioned under rupture into the pulmonary artery. When rupture occurs into the lung there may be either a rapid death from hemorrhage or a slower death from a "chronic pneumonia." Mediastinal ruptures offer no peculiar features, while those into the chambers of the heart resemble quite closely congenital heart disease. Spinal cord involvement by rupture is rare and unusually shows a rapidly advancing paraplegia. In rare instances rupture may take place into the stomach by dissection of the coats of the esophagus.

Conclusion. A study of 4000 aneurysms of the thoracic aorta has been made. The relationship to sex, age, age incidence in males and females was noted. The location of the lesion, the symptomatology, the physical signs, duration of symptoms, types of wrong diagnosis, location of ruptures and causes of death were studied.[1]

PROBLEMS IN HYPERTENSION—AN ATTEMPT TO CORRELATE HYPOTHETICAL AND PRACTICAL CONSIDERATIONS.*

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Starting from the fundamental observations of Bright down to modern studies in blood-pressure, blood chemistry, functional renal tests, renal pathology and physiology, there is perhaps no domain of internal medicine upon which more intensive work has been done, than upon the kidneys. Clinical hypertension in terms of renal pathology is one of the comparatively modern phases that is at present being constantly attacked and studied. Yet with all the amassed and voluminous literature and data on just this one phase of the problem—chemical blood investigations, experimental production of nephritis by injection of specific kidney poisons, and more recently by protein overfeeding; clinical studies of functional renal disease; finer studies of kidney pathology, there are but very

[1] The writer wishes to express his indebtedness to Dr. Aldred Scott Warthin, Director of the Pathological Laboratory, University of Michigan, for permission to examine the records of cases occurring in his service, and to Carl Vernon Weller, Professor of Pathology, University of Michigan, for reading the manuscript and many suggestions.

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few definite, indisputable, fundamental facts and concepts that have withstood assault. At least one positive statement may be made, namely that pathological hypertension in its final analysis is due to contraction of the systemic arterioles and capillaries, for as recently demonstrated (especially by Krogh), the immense capillary bed is also under the influence of nerves which can and indeed do profoundly influence the blood-volume in various areas of the body. Of immense importance is also the fact that capillary constriction does not necessarily go hand in hand with arteriolar constriction or with the independent contractility of capillary areas. For example, the arterioles of an area may show constriction, and the corresponding capillary bed may show dilatation. It seems to be the prime function of the capillary motor mechanism so to shift the intimate blood supply of tissues that up to a certain pathophysiological limit, the capillary blood supply, and therefore nutrition, is shifted where tissue economy needs it, be it in contracting muscles during work, in the gastrointestinal canal during digestion, and the kidneys at the height of their function. The interrelated nerve paths of these capillary motor nerves are at present entirely unknown.

It is fairly well recognized that arterial and arteriolar disease may be general and widespread, attacking the retinal and cerebral arteries, the aorta, kidneys, and pancreas and abdominal vessels; (general arteriosclerosis, atherosclerosis and arteriocapillary fibrosis) or the disease may attack and limit itself to the arteries of one organ predominantly and exclusively (usually in such instances the heart or the kidneys); or finally the disease may pick out and select just one or more of the principal arteries of an organ, for example, the aorta and coronaries, almost to the entire exclusion of the remainder of the cardiorenal vascular system.

In order to correlate certain clinical observations, I have divided hypertension as found clinically into certain groups; these cover the majority but by no means all hypertensive conditions. And it shall be my problem, in the light of physiological, pathological, experimental and clinical data, to try to discover, and, where necessary, to theorize frankly as to the possible basic, etiological "insult" for the hypertension.

I may interpolate here that instead of the term, essential hypertension, I prefer the terms hyperpiesis or functional hypertension, because if they have any precise significance at all, they refer to high blood-pressure without any known or discoverable pathological organic basis, and they are advisedly non-committal on the question of benignity or severity. I believe furthermore that essential hypertension is an especially inapt term because it has already been given so many meanings, hence it must be or should be exactly defined each time it is used. And when used in the sense of high blood-pressure without organic basis, functional hypertension conveys the idea more definitely.

In this paper hypertension will be regarded as consisting of a systolic blood-pressure of 150 or over.

Returning now to the groups we have:

1. *Abnormal Vaso-constrictor Influences Originating from the Higher Cerebral Centers.*

As is well known there are many pressor and depressor fibers in the nerves that reach the vasoconstrictor center in the medulla. Stimulation of the pressor fibers produces contraction of the peripheral vessels with increased blood-pressure, while stimulation of the depressor fibers produces a reverse influence, that is, peripheral dilatation with decreased blood-pressure. Furthermore mental work produces constriction of the skin arterioles, a depressor influence. "In both instances we must assume intracentral paths between the cortex and the center in the medulla."[2] As further bearing upon psychic vascular reactions, Krogh[1] has shown that an unnarcotized rabbit's ear properly prepared for microscopic study will not redden or blanch if the animal remains quiet. If, however, the animal be suddenly frightened or disturbed, often the ear first blanches and then reddens, palpable examples of arteriolar and capillary constriction and dilatation, respectively. Section of the dorsal sympathetic abolishes this reaction, hence the efferent paths probably follow these nerves. By analogy, it seems probable that pallor accompanying human emotions "is produced in the sympathetic tone of the small skin vessels, while blushing is due to a reflex relaxation of this tone."[1] Bearing these physiological and experimental facts in mind, it comes within the realm of clinical probability that an excitable, volatile individual, one who is constantly harried and worried and hurried in his daily routine may send abnormal excitatory influences from the brain through various efferent paths, thus inducing vasoconstriction, if only momentary, of the arteriolar and capillary beds, in other words, causing what we clinically measure as hypertension. On the other hand there are individuals who do not betray their excitement by external manifestations, but who make abnormal conscious attempts to hold themselves in check. Both are instances of what may be called potential vasomotor instability. I have not found them to be of an especial type of physique or habitus; they are neither predominantly stout, lean, obese, tall, or squatty. I conceive that such individuals may have hypertension, at least temporarily, even without the organic background of actual pathological cardiovascular renal disease; or if the latter already be present, such abnormal excitation may continue hypertension in such patients, indeed they may react more readily and consistently to any hypertensive influence. Thus the psyche of an individual is to be seriously reckoned with and weighed in its clinical application, in order to assess what may be termed the psychic component of such hypertensive cases. This viewpoint also serves to explain how patients of volatile or with

wilfully suppressed emotions—the typical rushing American business man, as an example of the former; the moody anxious individual of the latter—are so much benefited when they are ordered away from town and from business for a few weeks. Given a happy prognostic outlook, and provided there is no inordinately severe organic cardiorenal basis for the hypertension, they often feel very well and are capable of much physical exertion as in golfing, rowing and walking. This symptomatic improvement, especially in reference to dyspnea, dizziness and precordial uneasiness does not necessarily imply that there is always a corresponding decrease of blood-pressure but a degree of physical comfort, a happier outlook is given these patients which they retain when they are again enabled to take up their work in whole or in part.

2. *Reflex Influences Emanating from Aortic Disease.*

The aorta, as is known, is surrounded by many plexuses and nerve filaments, important branches of the vagus and sympathetic. I believe that the important significance of this rich net-work of nerves as originators and carriers of abnormal excitation to the vasomotor center has been almost entirely overlooked.

That hypertension can exist with cardiosclerosis, bu[t] without sufficient coincident renal disease to account for increased blood-pressure has again been recently emphasized by Moschkowitz.[3] In the 5 cases that he studied postmortem, the renal lesion was not of sufficient moment to be a factor in the hypertension; but widespread disease of the heart and its bloodvessels—aortitis, ventricular hypertrophy, scar tissue, coronary disease—was a feature in various amounts and degrees. Some clinical corroboration that isolated aortitis can cause hypertension is found in instances of luetic aortitis in which during the inflammatory recrudescence of the disease (a recrudescent aortitis), precordial pains, hypertension and bronchospasm occur, to again recede with recession of the inflammation. As Longcope states,[4] hypertension in such instances can scarcely be explained by pains or cyanosis "for pain is frequently absent, and dyspnea may continue for some time (fifteen to thirty minutes) after the sudden drop in blood-pressure which comes with the relief of acute symptoms." He speaks, however, of a paroxsymal type of dyspnea found in luetic aortitis, and compares this to what occurs in the experimental animal. I conceive that a lesser degree of bronchospasm and hypertension may occur in less acute cases. Thus in a patient of mine with typical well-compensated luetic aortitis, the usual blood-pressure was 170 systolic. Following a coryza, the patient developed asthmatic breathing, although not severe enough to be characterized as paroxysmal. During this time and until the symptoms came under control with less wheezing and coughing, the blood-pressure was from 150 to 160 systolic. Later, when the bronchial spasm and pain had practically disappeared, the systolic pressure was around 112. There was no

decompensation. This, then, is an instance of moderate hypertension in a patient with luetic aortitis and severe bronchial spasm, apparently induced by abnormal reflexes arising from a diseased aorta.

Instances of pure aortic disease with hypertension are typified in those cases of rheumatic aortic regurgitation in the young, with or without advanced ventricular hypertrophy. Here there is surely no evidence, clinical or pathological, of kidney involvement as a factor in the production of high blood-pressure, nor of course, does generalized arteriosclerosis play a role. The hypertension is not extreme, usually between 170 and 190; the diastolic pressure is very low or zero. Perhaps one in 3 or 4 cases of typical rheumatic aortic regurgitation, well compensated, with throbbing carotids and a Corrigan pulse presents this picture of hypertension. The vasomotors are labile. The blood-pressure may be 150 one day or at one time, and at the next examination, perhaps a few hours later, the pressure may be 180 or 190 with no difference in the physical or symptomatic status of the individual. What influences ventricular hypertrophy with its attendant cardiac hyperactivity may play in the production of this type of hypertension one cannot state dogmatically. At any rate, it seems probable that the prominent factor lies in the continuous "insults" produced by the continued tremendous aortic fling that hyperexcites the nerve mesh encircling the aorta. Perhaps ventricular hyperactivity with its blood fling is an added factor. The physical evidence of this aortic fling is readily derived by fluoroscoping a typical case of rheumatic aortic regurgitation.

The physiological principle that nerve impulses transmitted to the medulla act in maintaining the nerve tone of the vasoconstrictor center is now generally recognized,[1] yet that would scarcely explain how hyperexcitation of the nerve mesh surrounding the aorta in cases of rheumatic regurgitation and of syphilitic aortitis produces hypertension, for it is well known that undue stretching of the aorta excites the depressor, not the constrictor mechanism to action. On the whole, it seems probable that general tissue anemia from improper vascularization resulting from aortic disease, with its concomitant myocardial disturbance, may cause a pathophysiological response in the manner already pointed out, namely, sufficient vasoconstriction in some arteriocapillary areas to bring about clinical hypertension. In other words, although the nerve paths are unknown, vasoconstriction seems one of nature's peripheral provisions for deflecting more blood into an improperly nourished area by sufficiently constricting other arteriocapillary beds or bed, thus raising the blood-pressure.

3. *Reflex Influences Emanating from Coronary Disease.*

I refer here to individuals who present no general symptoms of advanced cardiorenal mischief, no abnormal signs, no dyspnea, no

cardiac enlargement, no decompensation, no urinary changes, no marked decrease, if any, of phthalein output, and who, on the whole, look robust and well preserved. They do present, however, two cardinal signs, hypertension (usually moderate) and precordial pains. The hypertension is not always constant, as is shown in the following case. Hypertension was present for a while some years ago and then disappeared. Indeed, although coronary disease was suspected from the beginning, quiescence of symptoms for years, normal blood-pressure and normal physical signs at later examinations lessened the impression of severe disease until death suddenly occurred.

The precordial pains of individuals in this group are usually not constant; they are marked by remissions and by occasional severe exacerbations in one of which the patient may suddenly die. The usual localizations of the pain are near the cardiac apex or at the midsternum, sometimes radiating to the back. They are present especially when the patient walks after meals, or when walking or driving against cold winds. Often the pains are so correlated with gastric symptoms, especially belching and pyrosis, that it is difficult, indeed at times impossible to decide which is the primary offender, the stomach or the heart. Such patients will be discussed more in detail in the following group (Group 4). A typical instance of temporary hypertension with coronary disease is herewith epitomized.

Dr. S., dentist, aged fifty-four years, was seen by me for the first time seven years ago. At that time the chief symptoms were precordial pains and moderate hypertension. The patient was considerably worried, and he worked very hard. He was an excessive tobacco smoker. The roentgen-ray and the electrocardiogram revealed nothing abnormal. He was told to quit smoking and to work less intensively. As a result, the precordial pains disappeared, the blood-pressure became normal and the patient was much more comfortable. I did not see him again until shortly before his fatal illness. In the interim he had felt comfortable, had only occasional pains and was able to go ahead with his work in normal fashion. The recent history was that during the past few months he had more marked precordial pains, especially when walking in windy weather. He had a very severe attack of pain four months and again two weeks ago; the latter followed some aggravation. Since then he had frequently to stop walking because of pains in his chest. Examination at his home revealed no dyspnea, the patient was able to lie flat in bed; the entire cardiovascular and pulmonary examination, including blood-pressure revealed no abnormality. He was kept in bed and for a few days was quite comfortable. One night he was taken with very severe pains in the chest and died within two hours. This case is an example of entirely negative physical findings except moderate hypertension some years ago. More

attention to the symptoms rather than to the negative physical findings may have aided in making the proper diagnosis, namely, coronary disease.

What seems of especial importance in patients of this group is that as far as clinical findings are concerned, the coronaries bear the main brunt of the arteriosclerotic process. When there is no evidence of widespread cardiorenal mischief it will naturally require corroborative postmortem examinations in order to rule out other important contributive pathological factors, especially of aortic, myocardial and renal disease.

As one instance of disease confined chiefly to the coronary system, but especially to the small artery supplying the auriculoventricular node, I wish briefly to quote a case of a woman, aged eighty years, with heart-block. The main coronaries were somewhat thickened but patulous, the artery that supplied the node was entirely sclerosed and calcified and was surrounded by a zone of degenerated musculature. The remainder of the heart, the myocardium, valves and aorta, was particularly well preserved and free from sclerotic changes. This again demonstrates how arteriosclerosis may selectively attack special arteries, not necessarily an entire arteriolar system; and when such arteries are vital to an organ like the heart, such isolated disease may produce severe cardiac symptoms and finally death.

How shall we explain hypertension in cases of assumed isolated coronary disease? Illuminating experiments by Starling[5] on the coronary bloodflow in the dog's heart show that if the coronary pressure be artificially raised, the heart, instead of becoming weaker, begins to revive, and the ventricular output increases, in spite of the necessarily increased work of the heart in overcoming the increased coronary blood-pressure. So also in another series of experiments, artificial increase of general blood-pressure increased the coronary output. Increased blood-pressure is apparently Nature's provision to increase the blood supply to the heart. Starling also states the vital necessity of proper coronary flow to insure proper oxygenation, proper tissue respiration and hence proper cardiac function.

What the actual mechanism is that increases blood-pressure in clinical instances of assumed isolated coronary disease it is impossible to state with exactitude. We know that the coronaries are richly surrounded and supplied with nerve plexuses and ganglia, and it seems highly probable that abnormal excitation originating from this rich nerve supply may reflexly excite and influence the vasoconstrictor center. On the other hand, coronary disease, when advanced, certainly decreases the blood supply to the peripheral tissues by depressing the pumping power of the heart. There is thus produced a struggle between different vascular fields. The sum total however must be a system with increased resistance;

thus a failing heart is countered in the peripheral vascular system by increased blood-pressure. This is again nature's provision for shifting blood-volume where needed for oxygenation purposes, always however with increased resistance, hence calling for more pumping power in order to force the proper amount through constricted arterioles, a true vicious cycle.

4. *Temporary Hypertension from Functional Cardiospasm.*

Patients of this group are usually stout individuals between thirty and fifty years of age who lead a busy active life, who continually rush about or are easily upset nervously, and who suffer from the clinical symptoms of mild cardiospasm: sensitiveness to pressure under the xiphoid, fulness and a tendency to belch. They usually bolt their food. There is sometimes a conscious feeling of food sticking for a moment at the cardia. Such cases of cardiospasm are mild and are not comparable to the occasional severe forms in which there is definite cardiospastic stricture of the cardia, with inability to pass normal sized bougies into the stomach. That mild cases exist, I demonstrated in at least one instance by roentgen-ray. The patient had epigastric tenderness, and distention and belching after meals. The barium mass after being swallowed was seen fluoroscopically to stick for several seconds at the cardia; there was reversed peristalsis for a few moments, the cardia then opened and the mass entered the stomach. While patients such as I have described have these outstanding gastric complaints, they also frequently complain of midsternal pains, which occasionally radiate to the left arm or to the back between the angle of the left scapula and the vertebral column. Another symptom which draws special attention to the heart is the fact that walking in the fresh air, especially after meals, is particularly apt to be followed by precordial and referred pains; added to this is moderate hypertension (usually from 150 to 180 systolic). Thus the clinical complex is one closely resembling coronary disease. But neither fluoroscopy, electrocardiography or phthalein output examinations, nor the ordinary methods of routine clinical examinations show any evidence of cardiac disease or decompensation.

A few examples will serve to illustrate this type: Mr. E. W. O., aged fifty years, has always been a quick and irregular eater, almost always bolting his food. For about two years, he has had mild dyspeptic symptoms; slight epigastric pain and belching after meals. His bowels are constipated. He has never vomited, his appetite has always been good. He is a moderate smoker. For about one year, he has had precordial pains, which of late radiate to the left arm and hand, and produce a sensation of tingling. Several times he has had to stop walking because of the precordial pains. He has also complained of headache and dizziness during the last six months; these symptoms are apparently not connected with his gastric complaints. Except for gonorrhea twenty-five

years ago, he has had no other infections. He passed a satisfactory life insurance examination one year ago. Of recent months he was told by his family physician that he has hypertension and true angina pectoris.

Examination reveals a stout individual. The pharynx is somewhat red, probably from smoking. He has some poor teeth. The systolic blood-pressure is 160, the diastolic 100. All the heart sounds are normal. There is no undue dyspnea or tachycardia after exertion. The lungs and reflexes are normal. There is no edema of the legs. Abdominal examination reveals slight but definite sensitiveness under the xiphoid. Orthodiascopic roentgen-ray examination reveals a normal sized aorta, with the heart lying flat upon the diaphragm. The electrocardiogram shows nothing of note. The urine is normal. The diagnosis of cardiospasm due to an irregular mode of eating was made. The precordial pains were regarded as caused by coronary spasm, not actual coronary disease. He was placed upon a bland, antacid diet and was admonished to eat his meals regularly and slowly. Atropin and an antacid powder were prescribed. He consulted me about once a week for several weeks. At the second visit, the systolic blood-pressure was 145; thereafter it came to normal (between 120 and 130 systolic) and remained so during the entire period of observation. The precordial and referred pains, and the dyspeptic symptoms quickly disappeared and when last examined, he felt perfectly well in every respect.

Mrs. H. S., aged forty years, has been suffering for years from gastric distention and belching, especially after improper diet. Several years ago and twice since, she had gastric attacks with temporary hypertension from 160 to 200; the blood-pressure became normal when indigestion ceased. Two days previously, the family physician found decided hypertension.

Examination: No cardiovascular symptoms; no previous infections; blood-pressure, 120 to 90; heart, very soft systolic at apex; somewhat accentuated second aortic at right base. Lungs, mouth, reflexes, urine, normal. Abdomen, slight epigastric sensitiveness. Orthodiascopic examination: First part of aorta slightly enlarged. Electrocardiogram: normal.

Diagnosis: No organic cardiovalvular disease, temporary hypertension, cardiospasm. Therapy: Patient may be active, avoid acids, bland diet, atropin sulphate, antacid powder. After a few days, the patient felt well and has continued so.

M. O., male, aged forty-three years, has always been very active, a quick eater, and never rests sufficiently. He is always thinking of business. He had been told he had hypertension, with pressure around 160. A trace of sugar was found once. He suffers from fulness and distention after meals and is much worried and does not know how to act about diet and general care. He has had no

previous infections, and no cardiac symptoms. He is walking most of the day and smokes three cigars daily.

Examination: Blood-pressure 160; very soft systolic murmur at apex; slight apical overaction. Abdominal examination, negative. Very lively reflexes. Urine normal. Orthodiascope, normal.

Diagnosis: No cardiovascular disease; hypertension from continual rushing and bolting food. Therapy: Atropin sulphate before meals, antacid powder after meals; take one hour for meals; go to country week-ends; rest in evening between six and seven. Prognosis: Very good.

January 20. Not improved because he did not follow directions.

April 29. Had been feeling well. Now again excitable and has headaches. Blood-pressure 140.

October 10. Slight recurrence of symptoms following nervousness about his father's health. Chief complaint, indefinite weakness in chest. Blood-pressure 150. Epigastric sensitiveness. Except for this spell, he had been well for months, with a normal blood-pressure.

It is difficult to correlate such abnormal excitation of the vagus branches supplying the lower esophagus and the cardiac end of the stomach, for cardiospasm is the outstanding clinical feature, as in itself a cause for hypertension, since physiologically vagus excitation results not in hypertension but in lowered blood-pressure. Perhaps both the cardiospasm and the hypertension are caused by abnormal cerebral impulses in these nervously excited individuals, and relief of the cardiospasm by atropin, and a quieter mode of living and of eating have the effect of calming these patients, thus relieving their hypertension. Therapeutic measures directed entirely to the gastric condition, proper food slowly eaten, rest for a while after meals, less rushing about, more mental quiet, not only relieves the gastric symptoms but also the hypertension. Atropin and an antacid powder are important therapeutic aids. The results of therapy are added proofs, I believe, that the source of trouble lies not in the cardiorenal system but in abnormal excitation of the vagus nerves that control the cardia.

5. *Hypertension with Auricular Fibrillation.*

This is well illustrated by the following case: Mrs. D., aged forty-seven years, does a great deal of physical labor in walking, carrying bundles and climbing stairs. She has had frequent attacks of bronchitis and of shortness of breath in recent years. Her climateric began two years ago. More recently she complained of severe dyspnea and had several fainting attacks. Examination shows auricular fibrillation, mild cyanosis, moderate hypertension and a heart slightly enlarged (roentgen-ray). The clinical diagnosis was moderate cardiosclerosis with superadded cardiac overstrain and climacteric hyperexcitability. She was given quinidin. The rhythm became normal after two days. The systolic blood-pressure

then was around 100 and remained at about that level during the time that she was under observation (several weeks). There was no decompensation with the lowered blood-pressure.

Hypertension in such instances of auricular fibrillation seems directly attributable to improper blood-mass distribution in the periphery, another instance of Nature's attempt to rectify circulatory instability by increasing pressure in some areas, thus shunting increased blood-volume in other more needed oxygen-poor areas, always, however, under the cardiac disadvantage of heightened blood-pressure. With normal rhythm and circulatory stability restored by quinidin, there is no longer need for Nature's safety provision and, where there is no advanced kidney disease, hypertension at once disappears.

6. *Hypertension with Endocrine Changes or with Exophthalmic Goiter:*

This refers especially to women at or near the menopause age and to cases of exophthalmic goiter. Regarding endocrine disbalance, hypertension here, at least in the beginning, must be regarded as of functional origin (so-called primary or essential hypertension), because nephritic or other pathological bases for the hypertension are almost always absent, and the hypertension is sometimes a temporary affair. Whether such hypertension can lead to actual nephritis is a very much debated question and will be discussed later. Theories regarding the cause of this type of hypertension are many; I need but mention the most popular, the hormones and adrenalemia, despite the fact that careful experimentation[6] had not revealed any abnormal amounts of adrenalin in the blood. There is however, some experimental evidence that a pituitary hormone may be responsible for pressor influences in the blood.[1] In the search for physicochemical and hormone factors, however, attention has been detracted from perhaps the fundamental pathological conception, namely, abnormal excitability of the nervous system. Nervous hyperexcitability in these individuals is well characterized in the main by sweats, flushes and general irritability. And in cases of exophthalmic goiter—in addition to and more intense than these latter symptoms—is the added factor of overviolent and overforceful ventricular action and the flinging of blood into the aorta. This factor as influencing the aortic nerve mesh has always been described (Group 2). It is in brief, my assumption that hypertension at the menopause and in goiter can be more logically explained upon a basis of obvious vasomotor instability, for which, at least, there are a few indubitable clinical facts. How much this vasomotor instability may directly affect and cause the restiveness by vascular changes in the cerebrum, and indirectly by causing a vicious cycle, such as described in Group 1, are questions still *sub judice*.

7. *Nephritic Hypertension.*

This, the most important division I have left to the last. Reference is here to assumed or proven widespread pathological changes in the glomeruli, whether the predominant change be a chronic interstitial, the decrescent type of the arteriosclerosis of the old, or the large white kidney. It is becoming increasingly recognized that the kidney changes rarely run "true to type," and that transition forms are frequent. It is also a matter of common knowledge that hypertension does not proceed *pari passu* with the amount of kidney damage found at necropsy. Indeed, I have not infrequently found frank nephritics that feel better with for them, abnormal hypertension—200 or over—than when the blood-pressure is around 180. Nor can this be purely psychical, for there may be less dependent edema and less dyspnea at the higher than at the lower systolic pressures. This may depend upon the principles already referred to, namely that the physiological response has been more vasoconstriction in some areas and hence more blood-volume shunted in needed areas, despite the hyperincrease in blood-pressure. As a rule we find hypertension in those with advanced changes in the glomerular tufts (actual arteriocapillary fibrosis in the pathological sense); while with disease predominantly confined to the larger renal vessels (the renal arteries and their ramifications, the vasa recti)—a picture general in old arteriosclerotics with widespread degeneration of the larger systemic, superficial and deep vessels, hypertension is often absent.

In advanced nephritis with hypertension, blood chemistry often shows varying increases of the non-protein nitrogenous products; it is assumed that in these individuals the retained products act as poisons and produce hypertension, abnormal arteriolar and capillary spasm and constriction. Yet even this assumption does not aid in determining how these poisons so act. Perhaps an analogy from plant life, and some suggestive physiological and experimental data may throw some light on this vexed and vexatious question. Plants get their nourishment by osmosis from rootlets which ramify through the wet earth; this nourishment is brought to the stalk or trunk. In a human being the rootlets are the arterioles; the moist earth, the capillary bed and tissues. Cushny[7] has estimated the number of glomeruli in the human kidneys as 2,000,000. If the twisted and bunched arterioles and capillaries so neatly packed by Nature into a small space of the kidneys were conceived as spread so as to resemble a capillary bed, one can only imagine the comparative immensity of such an arteriocapillary peripheral spread.

Arteriosclerosis has been variously described pathologically; the general pathological consensus of opinion is that it is not an inflammatory but a degeneration process. Disease of the glomeruli consists in thickening of the glomerular epithelium, and in fibrosis

and hyalinization and perhaps calcification of the glomerular tufts—"an arteriosclerosis in miniature."[3]

In an excellent experimental article, Richards[8] has emphasized the importance of nervous stimuli in the experimental production of vasodilatation and constriction of the glomerular capillaries. Nerve filaments, presumably branches of the splanchnic ramify to the glomerular tufts. Nerve stimuli (and chemical substances) have been shown experimentally to exert influences upon glomerular afferent and efferent vascular tone. This much for the local glomerular reaction. Conceiving the glomeruli as a whole merely as a large arteriocapillary bed, there is, after all, no basic difference between abnormal excitation from partial or complete disease of such a renal peripheral bed with resultant (reciprocal) vasoconstriction in another capillary motor area than is found in Nature's numerous provisions for vasodilatation in some parts of the body, and vasoconstriction in others. Splanchnic vasodilatation after a meal, and peripheral vasoconstriction in other areas is a common example. That retained kidney poisons would or might be added factors is not only conceivable but is also probable; for once a break in physiological continuity occurs and actual pathology begins, there is freer play for the commencement—and once begun—for the continuance of a vicious cycle. Nature would seem to have started hypertension in order to force more blood in an organ beginning to be or already crippled by pathological changes. In addition the other component of the vicious cycle, retained renal poisons, plays a large role in these individuals, a fact reflected in the blood chemistry. In the decrescent type of the old, predominantly renal arterial tree changes (the vasorecti and their branches), since the peripheral renal arteriocapillary bed is not disturbed, there is no tendency to abnormal peripheral arteriolar excitation and its consequent vasoconstriction. Indeed these comparatively large arterioles although stiffened by disease, allow sufficient blood-volume to pass through, provided of course the pumping mechanism is still sufficiently powerful and efficient. Lack of resiliency of hardened arteries does not necessarily interfere with their caliber; the latter interference comes only with advanced thickening and calcification.

Another vexed question in hypertension is, which is to be regarded as the primary factor? Does, or can, functional hypertension cause nephritis, or *vice versa*? Klotz[9] produced arteriosclerosis by suspending rabbits head down for prolonged periods. This experiment, though of course without comparable analogy in man, demonstrates perhaps that arteriosclerosis in the human being can be produced by too much pressure. An extremely suggestive point was made by MacCallum[10] in a review on the subject of arteriosclerosis. Reviewing experimental and other factors, he states that the most important etiological factors of arteriosclerosis are infections, intoxications

and unbalanced diets; that adrenalin injections produce arteriosclerosis (in rabbit's aorta) not merely as a hypertensive agent, but directly as a poison; that experimental methods of inducing hypertension may be divided into: (1) Mechanical means of raising blood-pressure; (2) chemical means of raising blood-pressure; (3) perverted diets. The first two he states, have failed to produce a type of arteriosclerosis comparable to that of the human being. Of the three groups, perverted diets have succeeded more regularly in producing arteriosclerosis experimentally, *especially when combined with mechanical disturbances*. Of these latter, increased blood-pressure (experimentally induced) is the only one of importance. In other words, increased blood-pressure produces arteriosclerosis experimentally only when combined with a factor (perverted diet) which causes actual kidney damage, *but alone it produces little or no change*. This statement is germane to our discussion, for it emphasizes well what I conceive happens clinically, that is, hypertension becomes a serious factor as a cause for nephritis only when there is with it some break, large or small, of physiological renal continuity. Therefore hypertension conceivably can cause nephritis, especially if one postulates the existence of an already pathologically damaged organ, whether such damage be microscopical or macroscopical. It is said that a 100 per cent normal kidney does not exist. This seems true in view of our knowledge that transient albuminuria is so common an accompaniment of febrile, tonsillar, exanthematous, toxic and other causes. Probably no one has escaped some such temporary kidney involvement who has lived to adult life. Who can say whether any permanent damage, no matter how minute, does not remain? In most cases the albuminuria clears up; in others, especially when tonsillar, febrile or other causes continue to recur, damage is added to damage until finally severe nephritic changes result.

And now, how shall we even theoretically explain permanent, continuing pathological damage in the vast majority of nephritic cases in which the toxic factor, whatever its nature, has ceased to act? The nephritis of scarlet is an excellent example; it undoubtedly is sometimes the beginning of a later severe nephritis, yet it usually takes years for severe damage to result. It seems to me that this is an important problem which we must attempt to elucidate. In this connection I wish to cite a suggestive article by Thalheimer[11] in which he attempts to prove that minute microscopical injuries to the cardiac valves, possibly the result of a mild toxemia, may finally eventuate, perhaps after years, in actual severe valvular damage, including verruci and even calcification. This he conceives results from slight, continuous mechanical insults—heart strain, improper minute aberrant currents, and so on, and not necessarily from superadded toxemias. The salient point is the assumption

of an original pathological nidus, the result of infection, protein poison, a toxic or dietetic factor, which causes loss of normal continuity, small or large, and which finally from *purely mechanical* reasons can eventuate into widespread pathological changes.

There are many theories regarding the fundamental cause of arteriosclerosis in the human being. Romberg[12] as well as Marchand[13] regard the cause as fundamentally due to nutritional disturbances in the arterial wall, following disuse. Moschkowitz[14] states that once hypertension is established many changes can be accounted for by "a mechanical stretching of the tissues with replacement fibrosis and eventually by hyalinization and calcification. The thickening of the intima, hypertrophy of the media and increase in the elastic fibers are probably in a great measure compensatory." This brings up the mechanical conception of the cause of arteriosclerosis, supported among older writers by Thoma, Traube, Rokitansky and Marchand. Adami[15] calls the process a "strain hypertrophy." Aschoff[16] does not believe in the disuse theory as the cause of arteriosclerosis. Moschkowitz[14] has suggested a mechanistic conception *without* however the important postulate of an *original pathological nidus*, however minute, as a starting point. With such a *locus minor resistentia*, given a tendency to hypertension, perhaps because of excitable temperament, or of abnormal renal products being retained, or indeed from any of the causes in the various groups already outlined, and in its trend, improper vascularization and improper nourishment to the kidney parenchyma, a vicious cycle may be started which in those disposed may conceivably produce far-reaching damage. And yet the beginning may have been as stated, a small microscopical change, the result of some temporary insult. Except as above mentioned, it is impossible to conceive how pathological mischief can continue after infections and toxemias have long ceased their acute damage, large or small. Replacement fibrosis, hyalinization, calcification, may after all be due to one fundamental cause, improper oxygenation with resultant improper tissue nutrition. Where there is already damage, even though microscopical, a *locus minor resistentia* is established. With this as a focus, all varieties of mechanical interference of the blood supply, contracted arteriocapillary areas, at the beginning not sufficient to cause clinical hypertension, can conceivably so further spread even microscopic glomerular damage that inevitably larger areas become affected. Finally there is that larger pathophysiological response of blood-volume shift so that ever larger arteriocapillary beds constrict to help shunt and supply the necessary blood-volume to the diseased glomeruli; at length the vasoconstriction is measured clinically as hypertension.

Why some individuals are "disposed" to kidney damage is again another moot question. Are some born with "weak kidneys" in a

morphological sense? Is it a fault in the germ cell? Is it a tendency to "bad vascular" tubing in the Osler sense, or is it after all poor terminal arteries, poor "rootlets," in the plant sense, rootlets that can no longer carry nourishment, and hence the organ slowly shrivels up and dries? These are queries which must for the present remain unanswered.

Summary. I have purposely been generic, hypothetical and sketchy, and have not entered into discussions of types of renal pathology. What I have attempted to do is to elucidate and correlate apparently contrary views, and have above all tried to find an underlying, fundamental cause which may perhaps tend to harmonize conflicting views; to show how functional changes may act and react upon an existent pathology, minute or gross; and how such morbid interactions, once established may eventuate into increasingly severe pathological destruction. Thus viewed, one may perhaps explain some common clinical facts such as the effect of toxins and infections in producing morbidity, and the effect of fundamental changes such as improper local vascularization in enhancing these morbid processes after the toxemia, using the term in its broadest sense, has long since run its course. Perhaps this problem can lend itself to experimental research; once establish that a pathological damage, already completed, can be made to spread by local or general vascular changes, changes which perhaps act fundamentally by undermining proper nutrition, and it will go far, I believe, in clearing up much that is misty and nebulous in the domain of cardiorenal-vascular pathology, and bring it in more direct line with actual clinical concepts and experience.*

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THE NON-CALCULOUS GALL-BLADDER.*

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The last decade has witnessed a surprising amount of literature dealing with the pathology and symptomatology of the infected gall-bladder. It may be deduced from these contributions that it is the element of infection in the gall-bladder that accounts for the symptoms rather than the incidental or accidental presence of calculi. Although the presence of calculi may add certain mechanical elements, and be the exciting agent, as in hydrops, yet the disturbed physiology and aberration of gastrointestinal function is due to the changes that have taken place in the wall of the gall-bladder rather than the presence or absence of calculi within its cavity. If we could imagine the introduction of sterile pebbles into a normal non-infected gall-bladder in all probability the patient would be unaware of their presence, except in the event of some mechanical phenomenon, such as the production of an obstruction, or pain incidental to passage through a duct.

There are three factors necessary for the production of gall stones. These are: (1) Infection, (2) biliary stasis of some degree and (3) foreign material. Whether that foreign material is clumped bacteria or mucin is relatively unimportant. Significant for our present consideration is the fact that stones cannot be formed without an existing infection. We are further constrained to believe that cholelithiasis is only an incidental and often a late factor, because if the bacteria were of a certain degree of virulence the changes in the wall of the gall-bladder would be of such severity as not to produce stones. It is when the bacteria are of such lesser virulence as to produce only minor changes in the gall-bladder wall that the stones are formed. In the strawberry gall-bladder of Moynihan stones are absent. This is likewise true in many other forms of cholecystitis, where the infection has produced atrophic and fibrotic changes.

In contemplating conditions of the gall-bladder there are certain anatomical and physiological facts concerning this organ that are of more than mere academic interest. It is a noteworthy fact that, although the gall-bladder is a hollow viscus with its fundus lower than its outlet, it is incapable of completely emptying itself, because of the inadequacy of the muscular coat. However, it

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undergoes periodic rhythmic contracture at about the rate of 8 to ten times a minute. The secretory pressure of the bile as it descends from the liver down the common duct, combined with the contractile pressure of the gall-bladder, is not sufficient to open the sphincter of Oddi, in spite of the fact that the secretion and liberation of bile from the liver are continuous. It is only by an automatic inhibition of the neuromuscular apparatus of the sphincter of Oddi that the sphincter can be released. In consequence there is only periodic flow into the duodenum, although continuous flow from the liver.

The nature of the bile, as it leaves the liver, is different from the bile found in the common duct and in the gall-bladder. The latter is thicker, darker and of a higher specific gravity, and chemical examination reveals mucoid and albuminoid materials. Rous and McMaster have shown that within twenty-four hours the cystic duct concentrates the bile from two to four times, while the gall-bladder concentrates the bile ten times. Thus we see that although its function may be subserved by the common duct, the gall-bladder has a function, or at least a physiological potentiality, and in that respect differs from the appendix, a vestigial organ that has no function at all.

These various factors, taken together, make the biliary apparatus one of great physiological and neuromuscular complexity. Because of this interdependence of various anatomical units, we can readily understand how any disturbance in one will soon cause reflex symptomatology in another.

From the viewpoint of our present consideration, the anatomy of the biliary apparatus commands our interest at two points. The first is the ductal arrangement at the duodenal end; the second is the arrangement of the lymphatics of the region. The somewhat complicated developmental history of the pancreas explains the close relationship between the head of the pancreas, the duct of Wirsung and the common bile duct. Depending on the eccentricities of development, the relationship of these ducts to each other and to the duodenum will vary. Consequently, Letuelle describes four types of papillæ of Vater.[1] However, the experiments of Mann have shown that while it is barely possible for pancreatitis to be caused by the influx of bile into the pancreas, or by contact infection from one duct into the other, this does not occur except under the most unusual conditions. Infection usually invades the pancreas by way of the lymphatics from the gall-bladder.

"A study of the lymphatics of the liver and gall-bladder demonstrates that there is no barrier between the intra- and extrahepatic lymphatics, but that the liver lymphatics pass unobstructedly into the gall-bladder, and the lymphatics of the gall-bladder pass directly into the liver substance through the area of attachment of the gall-bladder to the liver. The lymphatic system would seem to be

the connecting link in infections of the gall-bladder, liver and pancreas."[2]

Having thus demonstrated the close anatomical relationship between the liver, gall-bladder and pancreas, we are in a position to understand how one can become infected by virtue of an infection existing in any other of them. If the gall-bladder is the primary focus the liver will soon suffer in consequence, and the pancreas, at the other end of the lymphatic chain, will become involved by very much the same process as the development of a lymphangitis. Deaver carries this corollary to a logical conclusion, and says that if removing a focus of infection will clear up a lymphadenitis, then removing a diseased gall-bladder will most certainly cure a pancreatitis.[3]

On the other hand, the liver by a hematogenous route (it is interposed between the portal and arterial circulation) may be the first to be involved, secondary to a lower abdominal focus, as, for example, a diseased appendix. Bearing in mind the lymphatic distribution, we can trace very readily a secondary cholecystitis. There is thereby instituted the inception of a vicious cycle; for should the infective process at the point of commencement cease to be active, the diseased gall-bladder will continue to involve the liver, producing hepatitis. Here we have the crux of a formidable pathological process. The splendid work of Heyd and MacNeal has shown hepatitis to be a very definite pathological and clinical entity, becoming progressively more of a menace with the duration of its existence.[4] That it is productive of chronic digestive invalidism is clinically demonstrated by the fact that some cases of chronic cholecystitis are unimproved no matter what type of surgery may be done.

A significant factor in the diagnosis of non-calculous gall-bladder is the history of a gaseous indigestion, most often qualitative for certain fried or rich foods, without the occurrence of jaundice or of an attack of "gall-stone colic." In cases of longer duration the indigestion will often follow the ingestion of any food whatsoever, and therefore suggest the presence of a gastric ulcer. The picture of gall-bladder indigestion, however, lacks the almost mechanical precision with which events follow each other, which is ordinarily so characteristic of ulcer cases. The belching of large volumes of gas affords relief to the patient with gall-bladder disease, and after the gamut of carminatives has been run through, each being discarded as its worth has been spent because of too frequent use, it is not long before the sufferer learns to induce vomiting, to combat oppressive distention after eating. Many of these patients tell us that not infrequently they must excuse themselves from the dinner table, and after having successfully induced vomiting they are able to return and go through the rest of the meal in comparative comfort. We are all familiar with the old diagnostic axiom for gall-bladder disease, "fair, fat, forty and belching gas." Belching gas

remains the one most significant symptom, but with our better ability to interpret clinical symptoms we are recognizing a diseased gall-bladder to be the underlying pathology in an ever-increasing number of cases of indigestion, where the patient is not fat and not yet forty.

At laparotomy there are certain criteria in the absence of calculi that serve to indicate the presence or absence of pathology in a gall-bladder. Visualizing is necessary for a satisfactory examination of this organ; diagnosis based on palpation alone is apt to be fallacious; in any event, it is seriously open to question. Remembering the concentrating power of the gall-bladder, the presence of inspissated or thickened bile is in itself not indicative of the presence of infection. Ligamentous adhesions between the gall-bladder and the duodenum or the hepatic flexure of the colon occur with such frequency in cases where there is no other evidence of disease that their presence cannot indict the gall-bladder as pathological. What we consider as positive indications of disease are: (1) Loss of normal color. The normal color is olive green, with a bluish tinge. Exposure to air may cause changes in the color, therefore the gall-bladder should be inspected immediately on opening the abdomen, before other organs are explored. (2) A thickening of the walls is suggestive of infection, the degree of thickening being in direct ratio to the duration of disease. (3) The presence of pericholecystitis must be construed as indicative of disease within the walls of the gall-bladder; the evidence, however, must be present in addition to the so-called "normal cysticoduodenal and cysticocolonic ligaments" referred to above. (4) A deposit of saffron-colored fat over the fundus is not normal, and suggests mural infection. (5) A somewhat uncommon finding is a small red diverticulum on the fundus, and when present is indicative of sufficient pathology to warrant removal of the gall-bladder. (6) The single factor by itself most suggestive of disease is the presence of hyperplastic lymph nodes along the cystic duct and in the vicinity of Hartmann's pouch; when palpable, they are absolute indication of an infective process—either past or present. (7) On sectioning a diseased non-calculous gall-bladder, the mucous membrane is papillomatous in character, and often there is discernible the sparkle of tiny cholesterin crystals imbedded in the summit of the papillæ.

Conclusions. 1. Infection, not the presence of calculi, is the criterion of a surgical gall-bladder.

2. Hepatitis is almost an invariable, and pancreatitis a frequent, concomitant of biliary tract infection. Therefore, early surgery on an infective process is a wise procedure.

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PHENOLTETRACHLORPHTHALEIN IN THE STUDY OF LIVER FUNCTION.

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The development of a satisfactory liver function test is greatly to be desired. Numerous tests have been proposed, based either on a study of one of the specialized functions of the liver or upon the excretion of some foreign dye.

There is no object in reviewing at this time the first group of tests further than to recall that they have been disappointing and have failed of general adoption.

Of the second group we shall consider only phenoltetrachlorphthalein which has since its introduction held the promise of a satisfactory test, provided the method could be sufficiently simplified. This seems to have been accomplished, and it now remains to accumulate data for the purpose of standardizing the technic and of properly evaluating the findings. To this end a brief review of the methods and findings so far reported follows:

Review of Literature. The original technic, as proposed by Rowntree,[1] required the collection of total stools over a forty-eight-hour period, and the extraction and estimation of the dye present in this material. With this technic there was no unanimity of opinion regarding the value of the test, and owing to the technical difficulties it was soon discarded.

However, in 1916, MacNeil[2] revived the test, using the duodenal tube to collect the dye containing bile after the intravenous injection of 40 mg. of phenoltetrachlorphthalein. This enabled him to observe the appearance time of the dye in the bile, as well as to estimate the amount excreted in a two-hour period, and did away with the necessity of collecting and working with forty-eight-hour stools. He had difficulty at times, however, in establishing a satisfactory flow of bile. With this technic he found in 7 presumably normal cases an appearance time of from twelve to twenty-five minutes (Table I) and a two-hour output of from a trace to 10 per cent. In 5 cases of atrophic cirrhosis and 1 of extensive carcinomatosis of the liver the appearance time was increased, varying from twenty-eight to forty-five minutes, but the two-hour output was practically the same as in the normal controls. From these observations he concluded that the quantitative estimation of the

two-hour excretion is of little value, but that the appearance time is rather decidedly delayed in certain pathological conditions of the liver.

TABLE I.—APPEARANCE TIMES AND AMOUNT OF PHENOLTETRACHLORPHTHALEIN USED BY PREVIOUS OBSERVERS.

	MacNeil.	Aaron.	Williamson.	Higgins.	Friedenwald.	Piersol.	Boardman.
	7 cases.	16 cases.	15 cases.	5 cases.	95 cases.	15 cases.	10 cases.
Minimal and maximal	..	..	..	18	..	5.00	7
Initial appearance, times	..	..	..	21	..	11.00	10½
Minimal and maximal	12	14	16	55	..	8.75	9½
Maximum appearance, times	21	20	24	105	23	15.00	13
Amount of dye injected, mg.	40	50	50	50	75	150	150

MacNeil's report apparently aroused little interest, for it was not until 1921 that further reports appeared. In this year Max Kahn,[3] in a brief note on the Lyon-Meltzer method, stated that traces of phenoltetrachlorphthalein appeared in the bile of the duodenal content within twenty minutes of the time of injection. The amount of the dye injected is, however, not stated.

Later in the same year Aaron, Beck and Schneider[4] simplified the technic by first describing a method of preparing a stable solution of the dye, thus obviating the necessity of making a fresh solution for each test and second stated that by the administration of 500 cc of cool water by mouth after the tube had reached the duodenum a continuous flow of from 60 to 80 drops of bile-stained material a minute could be established and maintained for from one-half to three-quarters of an hour. They injected 50 mg. of the dye, and noted the initial appearance time and maximum appearance time of the dye in the drip from the duodenal tube. These times are determined by allowing the bile to drip into white porcelain dishes containing 40 per cent solution of NaOH, the initial appearance of the dye being indicated by a faint purplish ring at the point of contact of the bile and the alkali, and the maximum appearance by the point at which no further intensification of the color occurs with succeeding drops.

With this technic they found in 16 cases with no evidence of liver disease a maximum appearance time of from fourteen to twenty minutes (Table I), whereas in 7 cases with evidence of dis-

turbed liver function they found a maximum appearance time definitely prolonged. From their studies they conclude that the quantitative estimation of the dye excreted in a given time is of no value, because of the factor of leakage into the lower bowel, that a maximum appearance time of more than twenty minutes is suspicious of liver involvement, and that the test may be of great value in following the course of liver diseases.

Piersol and Bockus,[5] in 1923, followed in general the technic of Aaron, but used 150 mg. of the dye instead of 50, noted the time of initial appearance of the dye, the time of maximum appearance and estimated the total two-hour output. They report 50 cases, 15 presumably normal and 35 suffering from various pathological conditions, and divide them into four groups solely on the basis of the quantity of dye excreted in the two hours: Thus, in Group I are the 15 presumably normal cases, showing a two-hour elimination of from 19 to 27 mg. of the dye, an initial appearance time of from five to eleven minutes and a maximum appearance time of 8.75 to 15 minutes (Table I). In Group II 17 cases are presented with a two-hour excretion of from 10 to 19 mg., an initial appearance time varying from seven to twenty-five minutes and a maximum appearance time varying from ten to twenty-six minutes. In Group III there are 8 cases with a two-hour output of from 5 to 10 mg., but here again the initial appearance time varies from seven to twelve minutes, and the maximum appearance time varies from eleven to twenty-four and a half minutes, and finally in Group IV there are 10 cases with a two-hour excretion of less than 5 mg., with an initial appearance time of from eight to twenty-four and a half minutes and a maximum appearance time of from fourteen to twenty-nine and a half minutes.

From these findings they conclude that in a general way a delay in the appearance time is proportionate to a decrease in the two-hour output, and that the quantitative estimation of the two-hour output is of greater importance than the appearance time, although both should be considered. It is their impression that the two-hour output will show lesser grades of functional disturbance than will the initial and maximum appearance times.

Higgins,[6] using 50 mg. of the dye, noted the initial and maximum appearance times, also the disappearance time, or the time at which the dye ceased to appear in the bile, and finally estimated the total amount of dye excreted. He concludes from a study of 5 presumably normal cases that the initial appearance time varies from eighteen to twenty-one minutes, and the maximum from fifty-five to one hundred and five minutes (Table I). He also found the disappearance time to vary from ninety to one hundred and thirty-five minutes and the total output to vary from 40 to 48 per cent. In 16 pathological cases he found delay in the appearance times and decrease in the total output in those in whom liver

disturbance might be suspected, and concludes that the method is of value in the study of liver conditions.

Friedenwald,[7] later, in 1923, using 75 mg. of the dye, reports on 93 cases, and concludes that the normal average initial appearance time is thirteen and four-fifths minutes and that a delay of more than twenty-three minutes indicates hepatic disease or mechanical obstruction (Table I).

Dakin and Graham,[8] in a combined clinical and experimental study, were unfavorably impressed, but especially with the quantitative estimation, because of the various factors which seemed to prevent a complete collection of the liver bile by means of the duodenal tube.

Williams[9] studied 20 pregnant women, using 50 mg. of the dye, and found that the normal maximum appearance time varied from sixteen to twenty-four minutes (Table I). In 5 showing albuminuria 3 gave normal reactions and 2 a delayed appearance time. He was unable to draw any conclusions from this study.

While these reports dealing with the duodenal-tube method were appearing, Rosenthal,[10] recognizing some of the defects of this technic, developed his method. His experimental work was based on the theory that as the liver is practically the only organ involved in the elimination of phenoltetrachlorphthalein, and as the dye only appears in the urine where there is evidence of decreased output by the liver, it is probable that there is retention of the dye in the blood when liver function is impaired. With this idea in mind, he studied a series of normal dogs and found that after the intravenous injection of 5 mg. of phenoltetrachlorphthalein per kilo of body weight there was an immediate rise of the dye in the plasma to approximately 10 per cent, with a rapid fall to only a trace or complete disappearance within fifteen minutes. When the liver was experimentally damaged there was an immediate rise to from 15 to 30 or more per cent and the values remained elevated for a prolonged period, 11 per cent having been recovered almost two hours after injection. There was evidence that the curves of retention paralleled the degree of impairment of liver function.

These facts having been established, he applied the test clinically,[11] injecting 5 mg. per kilo dissolved in 25 to 30 cc of physiological sodium chloride solution into a superficial vein of one arm after first collecting about 8 cc of blood. Fifteen and sixty minutes after this injection 2 to 4 cc of blood was withdrawn from the other arm, and allowed to clot. The plasma was pipetted off and put into separate small test-tubes of uniform size and 1 drop of 5 per cent NaOH added to each tube. Phenoltetrachlorphthalein, 10 mg., was now added to 100 cc of water, this strength representing approximately the concentration that would be reached if all the injected dye remained in the plasma. With the plasma obtained before the injection of the dye, a series of standards was prepared in small

test-tubes of similar size, ranging from 25 to 3 per cent. The plasma in which the amount of dye was to be determined was matched with these standards.

Using this technic, he examined 10 normal cases and 10 cases of extrahepatic disease, and in these 20 cases he found from 2 to 6 per cent of the dye present at the fifteen-minute interval; practically complete absence at the sixty-minute interval. In 5 cases of carcinoma of the liver, 3 of cirrhosis and 9 of miscellaneous liver diseases, there was a more or less marked retention of the dye at the fifteen-minute and one-hour interval, the degree of retention apparently giving an index of the functional disturbance of the liver. He encountered no general reactions, but did have frequent induration of the vein at the site of injection and in 2 cases localized thrombosis, which persisted for several days. In the 20 normal and control cases no dye appeared in the urine, whereas in the pathological cases all but 4 showed dye in the urine, but not in proportion to the concentration in the blood.

From this work Rosenthal concluded that this method of testing liver function depends on the ability of the liver to remove the dye from the blood stream, that it is not difficult or time-consuming, that there is retention of the dye in the plasma in cases of hepatic disease and that the results are quantitative and probably give an index of the functional capacity of the liver.

In 1923 Rosenfield and Schneider,[12] practically following Rosenthal's technic, studied 6 normal pregnant women and 7 with neurotic or toxic vomiting, and confirmed Rosenthal's conclusions both as to the rate of disappearance of the dye in normal cases and to the value of the test in studying hepatic disease.

From this review it is evident that practically all investigators who have so far reported are convinced of the value of phenoltetrachlorphthalein in the study of liver function. However, considerable work remains to be done and several points settled before the test can be generally adopted. Thus, in the duodenal-tube method a standard amount of the dye must be employed, the limits of normal variation in the appearance times must be defined and the value or lack of value of the quantitative estimation of the dye output determined. Again the relative merits and demerits of the Rosenthal and duodenal tube methods must be established and the indications or contraindications for the use of one or the other method defined, and finally there must be accumulated a mass of carefully studied clinical material controlled by pathological examinations before the real value of the test can be established.

Clinical Studies. In an effort to clarify some of these points we undertook the following study of normal and pathological cases, using in the majority both the Rosenthal and duodenal-tube methods. In the former we followed the original technic without essential modification; in the duodenal-tube method we also followed the usual technic, using 150 mg. of the dye, as suggested by Piersol.

We made no quantitative estimations of the output of the dye by the duodenal-tube method, as we convinced ourselves that it was impossible to collect uniformly by the duodenal tube all the bile excreted by the liver over any given period.

There are two factors which make this impossible. The first is the indeterminate amount of bile that may find its way into the gall-bladder during the period of the test and thus escape collection by the tube. We have repeatedly demonstrated upon dogs and operative cases that large amounts of the dye are present in the gall-bladder bile from fifteen minutes to several hours after injection. It may be objected that if we had had the tube in the duodenum and the drip established no freshly secreted liver bile would have entered the gall-bladder, but that it would all have been discharged into the duodenum. This does not seem probable and certainly cannot be accepted without ample proof. However, even disregarding the first factor, the second, that of leakage into the small bowel, is sufficient. This leakage we have demonstrated by recovering large amounts of the dye in the stools following a routine test in which, however, the drainage was continued beyond the time of disappearance of the dye from the bile.

Piersol and Bockus, however, concluded that the quantitative estimation of the two-hour output was a more accurate indication of slight functional disturbances than the appearance time. Yet if we study their charts it seems apparent that they have accepted without confirmatory proof that the quantitative estimation is of prime importance. Thus they have divided their cases into four groups solely on the basis of the two-hour output. On this basis 35 cases fall into the three groups apparently having some disturbance of liver function, but of these 35 cases 17, or 48.5 per cent, have an initial appearance time falling within their limit of normal, and of these 17 cases 13, or 37.1 per cent, have also a maximum appearance time within their limits of normal. On the other hand, they fail to present any clinical or pathological evidence of liver disease in these cases with normal appearance times. We, therefore, cannot agree with Piersol and Bockus or with Higgins as to the value of the quantitative estimation of the dye, but do agree with Friedenwald, Aaron, Graham and MacNeil that it is useless as a functional test.

Using 150 mg. of the dye, we found (Table II) by the duodenal-tube method in 10 presumably normal cases an initial appearance time of from nine and a half to thirteen minutes. These figures agree very closely with those reported by Piersol, who used the same amount of dye, and are somewhat lower than those of the other observers who used smaller amounts of the dye. Higgins' figures alone are not in keeping with the general average and cannot be explained.

TABLE II.—RESULTS OF THE ROSENTHAL AND DUODENAL-TUBE METHODS IN TEN APPARENTLY NORMAL CASES.

Case No.	Rosenthal.		Duodenal tube.	
	Per cent at 15 minutes.	Per cent at 40 minutes.	Initial appearance time.	Maximum appearance time.
I	5	0	7	9½
II	5	0	7½	10
III	5	0	8	11
IV	5	0	8	11
V	6	0	8½	10
VI	5	0	8½	11
VII	6	0	9	10
VIII	6	0	9	12
IX	5	0	10	12
X	8	0	10½	13

With the Rosenthal method these same 10 apparently normal cases gave fifteen-minute values of from 5 to 6 per cent, with the exception of 1 case, which showed 8 per cent (Table H). At the forty-minute period after injection the dye was absent from the serum in all. These findings agree with Rosenthal's, except for the 1 case showing 8 per cent at fifteen minutes, and it is of interest that this same case gave the highest values for the initial and maximum appearance times of the series.

It is, therefore, evident that our findings agree with those of Rosenthal and Piersol, and especially that the two tests seem to show an absolute parallelism.

TABLE III.—RESULTS OF THE ROSENTHAL AND DUODENAL-TUBE METHODS IN TWENTY-TWO CASES OF CHRONIC CHOLECYSTITIS.

Case No.	Rosenthal.		Duodenal tube.	
	Per cent at 15 minutes.	Per cent at 40 minutes.	Initial appearance time.	Maximum appearance time.
I	4	0	7	11
II	6	4	8	10½
III	8	0	8	11
IV	8	0	9	12½
V	6	0	9½	11
VI	5	0	9½	11
VII	..	..	9½	12
VIII	8	0	9	14
IX	..	..	9	14
X	6	0	10	12½
XI	6	0	10	14
XII	8	2	10	15
XIII	6	0	10½	13
XIV	8	0	10½	16
XV	9	0	11	13
XVI	9	2	11	16
XVII	10	2	12	16½
XVIII	8	0	12½	15
XIX	9	2	13	16
XX	10	4	13	18
XXI	10	4	14	18
XXII	10	4	15½	17½

Table III shows the results of the tests in a series of 22 cases of chronic cholecystitis in which more or less functional disturbance was to be anticipated. The most striking feature of this study is the almost absolute parallelism of the two tests, Case II being the only exception and remaining as yet unexplained.

In 10 cases of definite liver disease the same parallelism between the findings by the two tests and the apparent ability of either test to demonstrate disturbed liver function is evident in Table IV.

TABLE IV.—RESULTS OF THE ROSENTHAL AND DUODENAL-TUBE METHODS IN TEN CASES OF DEFINITE LIVER DISEASE.

Case No.	Clinical diagnosis.	Rosenthal.		Duodenal tube.	
		Per cent at 15 minutes.	Per cent at 40 minutes.	Initial appearance time.	Maximum appearance time.
I*	Cholecystectomy five years before; recurring attacks of pain and jaundice since	10	6	8¼	11
II†	Acute hepatitis	15	2	9	14
III	Cholecystectomy	8	0	12	15
IV‡	Cirrhosis, cardiorenal	15	10	12½	16
V	Cirrhosis, syphilis	16	12	15	25
VI	Hanot's cirrhosis	9	9	15½	31
VII	Hepatitis, acute	12	12	16½	18
VIII	Colangitis	..	..	17½	27
IX	Cirrhosis	16	14	19	28
X	Hepatitis	20	16	24	28

* Rosenthal test performed a week later than the duodenal tube test, and was followed in a few days by an attack of pain with jaundice.

† Rapidly clearing acute hepatitis. Duodenal tube test done twenty-four hours after the Rosenthal.

‡ Rosenthal test done day before duodental tube test.

In Table V are tabulated the findings in a group of miscellaneous pathological conditions apparently free from liver involvement. Here again is shown the close parallelism between the two tests.

TABLE V.—RESULTS OF THE TWO TESTS IN FIVE PATHOLOGICAL CASES WITHOUT EVIDENT LIVER INVOLVEMENT.

Case No.	Clinical diagnosis.	Rosenthal.		Duodenal tube.	
		Per cent at 15 minutes.	Per cent at 40 minutes.	Initial appearance time.	Maximum appearance time.
I	Ileocolitis	5	0	7	10
II	Healed duodenal ulcer	4	0	8	10
III	Hyperacidity	6	0	8¼	11
IV	Duodenal ulcer	5	0	8½	10
V	Cardiorenal anemia	5	5	10½	15

Conclusions. 1. In phenoltetrachlorphthalein we have a valuable means of studying the functional activity of the liver.

2. The findings by the duodenal-tube method and the Rosenthal method are apparently of equal value and significance.

3. Therefore the choice of method ordinarily rests with the individual preference of the investigator, except in cases of common duct obstruction, or when for one reason or another the passage of the tube is contraindicated or impossible. Our own preference is for the duodenal-tube method whenever possible, because of the natural objection on the part of the patient to the injection of large amounts of highly colored material intravenously and because of the danger of induration and thrombosis with these large injections which are necessary in the Rosenthal method.

4. With the duodenal-tube method we would recommend the adoption of the 50-mg. dose as the standard, because there is no apparent advantage in the larger doses.

5. Because of the impossibility of collecting all the bile excreted over a given period quantitative estimations by the duodenal-tube method are of no value.

6. With 150 mg. of the dye an initial appearance time of eleven minutes or over, and a maximum appearance time of fourteen minutes or over, would seem to indicate liver disturbance. In normal cases the time between the initial and maximum appearance of the dye rarely exceeds three minutes. In pathological cases this time is frequently but not uniformly increased. It is our impression that the maximum appearance time may occasionally be influenced by the factor of dilution by the gastric contents (the water given the patient to drink) and, therefore, be less reliable than the initial appearance time.

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OBSERVATIONS ON THE TREATMENT OF PRIMARY AND SECONDARY SYPHILIS.*

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The old dictum that the most successful practitioner of medicine is he who most successfully treats syphilis was never truer than today. Fourteen years of empiricism with the arsenicals has at least taught us the folly of reliance only on this chemical in the treatment of lues, also the archaism of the belief that syphilis can be satisfactorily treated by mercury alone. Certain outstanding facts have become apparent: (1) The necessity of early diagnosis and the urgency of intensive, efficient treatment in order to cure, and the irreparable evil of single or small dosage and desultory treatment. (2) The superiority of maximum to fractional dosage of salvarsan and neosalvarsan or their substitutes as a sheet-anchor in therapy. (3) The increased incidence of arsenical reactions. (4) The decreased effect on the Wassermann and other serological reactions and an increment in the number of "Wassermann-fast" cases. (5) The apparent dissatisfaction with the arsenicals, as evidenced by resort to a galaxy of other drugs, notably, mercury, bismuth, silver- and sulphur-arsphenamin. (6) The advisability of synchronous or supplemental treatment with mercury and other drugs. (7) The necessity of efficient "follow-up" on blood and spinal fluid.

In this connection I cannot refrain from directing attention to former reports in 1916[1] by myself on the treatment of syphilis.[2] It seems to be a fact that the results then obtained have not been surpassed and probably not equalled by the substitutes of old salvarsan and neosalvarsan or by any modifications of the technic employed at that time, which followed implicitly the dicta and precautions laid down by Ehrlich. At that time it was our experience and I think generally conceded that salvarsan was more effective than neosalvarsan, particularly so far as the Wassermann reaction was concerned, which, after all, is an indispensable criterion in the successful treatment of syphilis. Then it was observed that if patients in the primary and secondary stages of the disease have a sufficient number of injections of salvarsan or neosalvarsan to secure a negative Wassermann, a possibility in 95.2 per cent of cases, it remained negative in the vast majority of patients for one to three years and in some cases for five and a half years, even though no mercury was used. In a few patients with chancres that we have been able to follow, the blood and spinal fluid Wassermanns have remained negative in the absence of any other treatment for twelve

* Read before the Philadelphia County Medical Society, May 14, 1924.

Conclusions. 1. In phenoltetrachlorphthalein we have a valuable means of studying the functional activity of the liver.

2. The findings by the duodenal-tube method and the Rosenthal method are apparently of equal value and significance.

3. Therefore the choice of method ordinarily rests with the individual preference of the investigator, except in cases of common duct obstruction, or when for one reason or another the passage of the tube is contraindicated or impossible. Our own preference is for the duodenal-tube method whenever possible, because of the natural objection on the part of the patient to the injection of large amounts of highly colored material intravenously and because of the danger of induration and thrombosis with these large injections which are necessary in the Rosenthal method.

4. With the duodenal-tube method we would recommend the adoption of the 50-mg. dose as the standard, because there is no apparent advantage in the larger doses.

5. Because of the impossibility of collecting all the bile excreted over a given period quantitative estimations by the duodenal-tube method are of no value.

6. With 150 mg. of the dye an initial appearance time of eleven minutes or over, and a maximum appearance time of fourteen minutes or over, would seem to indicate liver disturbance. In normal cases the time between the initial and maximum appearance of the dye rarely exceeds three minutes. In pathological cases this time is frequently but not uniformly increased. It is our impression that the maximum appearance time may occasionally be influenced by the factor of dilution by the gastric contents (the water given the patient to drink) and, therefore, be less reliable than the initial appearance time.

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OBSERVATIONS ON THE TREATMENT OF PRIMARY AND SECONDARY SYPHILIS.*

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The old dictum that the most successful practitioner of medicine is he who most successfully treats syphilis was never truer than today. Fourteen years of empiricism with the arsenicals has at least taught us the folly of reliance only on this chemical in the treatment of lues, also the archaism of the belief that syphilis can be satisfactorily treated by mercury alone. Certain outstanding facts have become apparent: (1) The necessity of early diagnosis and the urgency of intensive, efficient treatment in order to cure, and the irreparable evil of single or small dosage and desultory treatment. (2) The superiority of maximum to fractional dosage of salvarsan and neosalvarsan or their substitutes as a sheet-anchor in therapy. (3) The increased incidence of arsenical reactions. (4) The decreased effect on the Wassermann and other serological reactions and an increment in the number of "Wassermann-fast" cases. (5) The apparent dissatisfaction with the arsenicals, as evidenced by resort to a galaxy of other drugs, notably, mercury, bismuth, silver- and sulphur-arsphenamin. (6) The advisability of synchronous or supplemental treatment with mercury and other drugs. (7) The necessity of efficient "follow-up" on blood and spinal fluid.

In this connection I cannot refrain from directing attention to former reports in 1916[1] by myself on the treatment of syphilis.[2] It seems to be a fact that the results then obtained have not been surpassed and probably not equalled by the substitutes of old salvarsan and neosalvarsan or by any modifications of the technic employed at that time, which followed implicitly the dicta and precautions laid down by Ehrlich. At that time it was our experience and I think generally conceded that salvarsan was more effective than neosalvarsan, particularly so far as the Wassermann reaction was concerned, which, after all, is an indispensable criterion in the successful treatment of syphilis. Then it was observed that if patients in the primary and secondary stages of the disease have a sufficient number of injections of salvarsan or neosalvarsan to secure a negative Wassermann, a possibility in 95.2 per cent of cases, it remained negative in the vast majority of patients for one to three years and in some cases for five and a half years, even though no mercury was used. In a few patients with chancres that we have been able to follow, the blood and spinal fluid Wassermanns have remained negative in the absence of any other treatment for twelve

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years. In reviewing these results and contrasting them with the experience of today, using modified technics and the present-day arsenicals and other drugs substituted for 606 and 914, we are struck with the inferiority of results, clinically and serologically, the greater number of "Wassermann-fast" cases, the increase in severe reactions, notably dermatitis and the increased necessity for supplementary mercurial therapy. What is the explanation? Either the substitutes for salvarsan and neosalvarsan are not so potent as the originals or the technic of administration today is not so good. I believe both are true, and the sooner we return to the original instructions for preparation and injection, specified by Ehrlich and his co-workers striving for Ehrlich's ideal "therapia sterilisans magna," the better it will be. We must look forward to an improved preparation, more potent as a spirochetocide and less toxic, whereby more intensive and larger dosage can be employed, and fractional or small dosage of the present day preparations may be obviated.

I am confident that a large proportion of the reactions following the intravenous administration of the arsenicals is due to erroneous present-day technic of administration, and believe that employment of solutions isotonic with the blood, freshly and properly distilled sterile water of the proper temperature for dissolving and diluting the drug, and immediate slower injections and the elimination of mercury synchronously with the administration of the arsenicals, will materially reduce the number of serious reactions. Doubtless some are due to individual idiosyncrasies. In our experience the percentage of reactions from neosalvarsan exceeded that from salvarsan, but were not so severe; and in neither case were they comparable with the reactions obtained from the present-day substitutes. In recent years reactions have been minimized by resort to fractional doses more frequently administered, but likewise with diminished therapeutic effect.

Nitritoid crises, neurorelapses and jaundice due to an injury to the liver by the toxins of syphilis, have decreased in frequency, but the skin reactions have increased materially. Insufficient attention is given to gauging the dose proportionally to the body weight. Too much stress cannot be laid on the observance of the contraindications; nephritis, not due to lues, other concurrent infections and jaundice or skin reactions incident to previous injections. The production of or the contraindication offered by nephritis should be easily avoided by routine urinalysis before the first injection and the morning after each injection of the arsenicals.

The administration and value of epinephrin for the control of nitritoid crises is too well known for further comment. Sodium thiosulphate intravenously, at first daily and later on alternate days, in doses ranging from 5 to 25 grains, seems to possess definite antidotal properties and promises to be of exceptional merit in arsphenamin dermatitis.

The paramount requisition for cure in the treatment of syphilis is early diagnosis. If that diagnosis can be made in the primary stage before the advent of a positive Wassermann reaction, and that can and should be done in about 90 per cent of patients, the number of incurable cases should be very small. On the contrary, if the diagnosis be delayed until after the serological test becomes positive, the case must be regarded and treated as one of secondary syphilis, and the prognosis as to ultimate cure becomes at once and for all time, far less hopeful. Granted that, although it is possible in the majority of patients, to diagnose primary and secondary syphilis, clinically, no medical audience today needs to be reminded of the indispensable utility of the dark-field microscope for the only sane and safe management of doubtful sores or the examination of aspirated fluid from the regional lymph nodes in the event of negative findings from suspicious ulcers, or the Wassermann reaction, not so much from the diagnostic as from the prognostic and treatment standpoint.

Over ten years ago we pointed out[3] "that there should be some means of coöperation of Wassermann workers for standardization and uniformity of methods, to be adhered to as long as they are justified by clinical results, with the acceptance from time to time of such advances in technic as may be approved. In this way only will the serological syphilis reaction retain the confidence that its intrinsic value merits." Apropos of the discredit which at times has attached to this most valuable test of syphilis, it should be impressed today that the incidence of false positive Wassermann reactions with cholesternized antigens has been reduced or removed by Kolmer's new antigen, and his persevering researches in this work is an important step in the right direction for the standardization of the serological diagnosis of syphilis.

Finally, I should like to enter a vigorous plea against the use of the term "Wassermann" in the presence of patients. It is one of the most deplorable mistakes in modern medical practice. There is no more reason for the patient to know why he is having his blood tested or the result thereof, than there is to be informed of his routine blood count, biochemical test or urinalysis. Some, as the result of persistently positive Wassermanns, commit suicide, go crazy or become physical, mental and moral wrecks. Others, after a short course of treatment and a negative blood test, are prone to regard the decision too lightly, assume they are cured, neglect further necessary follow-up treatment with the inevitable result of latent tertiary or neurosyphilis.

The prophylactic, or what our ecclesiastical brethren are wont to call the early, treatment of lues, in addition to soap and water cleansing and bichloride or mercury washes, consists mainly in the male of the introduction of 33⅓ per cent calomel ointment into the urethra and smeared over the genitalia within an hour of exposure.

The value decreases practically to *nil* in eight hours. In the female, owing to the difficulty of carrying out the calomel ointment applications, three intravenous injections of salvarsan should be given. This should also be done in the male if the routine prophylaxis has not been applied in the first hour.

Irrespective of rules, methods and drugs, each case of syphilis is a study unto itself as to the best and most efficient method of treatment. Here as in every other phase of medicine the patient as well as his disease must be intelligently treated. My procedure in primary and secondary syphilis, as well as it may be defined is as follows: The Wassermann reaction is the great therapeutic divide. Its importance lies not so much in the field of diagnosis as in the realm of prognosis and treatment. It is utterly illogical and nonsensical to treat a patient with a chancre and a negative Wassermann that does not become positive under treatment, as vigorously and as long, as another patient with a positive Wassermann, irrespective of degree. Therefore, from the standpoint of treatment, we divide our patients in the primary and secondary stages of lues into two groups, those with negative, that is, in the early primary stage, and those with positive serological reactions, that is, the late primary and secondary stages.

In the first group, with efficient treatment, the prognosis is very good and cure can be expected in the vast majority of cases. This is the time to begin the treatment of syphilis, when it may be aborted and the patient can usually be assured an absolute cure. Three to 6 full-sized intravenous injections of salvarsan, neosalvarsan or their substitutes at weekly intervals are administered, the first given immediately on the day the patient first presents himself, for I regard the syphilitic in this stage of the disease just as much an emergency proposition from the standpoint of treatment and cure as the diphtheritic so far as antitoxin is concerned. Before each injection the blood should be taken to detect the possible advent of a positive Wassermann reaction, which occurrence will markedly influence subsequent treatment. I have never observed the development of syphilis in a Wassermann-negative patient in this group when old salvarsan or neosalvarsan was used employing as few as 3 injections, even without mercury. I have followed a few of these cases for twelve years, during which time they have never exhibited clinical evidence of syphilis and today present negative bloods and spinal fluids. I am not at all convinced that supplemental mercurial treatment is demanded in this group.

Excision of the chancre is not necessary, but may be done if located on the prepuce or if complicated by phimosis. The application of calomel or one of the arsenicals to the chancre itself, though of little value, will relieve the mind of the patient.

The second group, irrespective of whether the patient is in the late primary or secondary stage of the disease, furnishes the real test of our knowledge of the treatment of syphilis. The concensus

of opinion of the leading syphilographers at present is that this Wassermann-positive group should be treated continuously for one to two years even though the blood test is rendered negative in a few weeks. With this verdict I am heartily in accord and feel that too much reliance in the past has been placed on the production of a negative Wassermann from a few arsphenamin injections, administered in a desultory manner, and supplemented or not by a short or obviously inadequate course of mercury. In this group, not less than 6 full-sized doses (0.1 gm. per 30 pounds body weight) of salvarsan or neosalvarsan should be given at weekly intervals, in the absence of contraindication. Two to three weeks thereafter, the Wassermann should be determined, but irrespective of that finding, a second series of not less than 6 injections of the arsenicals should be administered, followed by another serological blood test. Should this be negative as invariably will be the case, an examination of the spinal fluid by Wassermann, globulin, cell count and colloidal-gold tests, should be advised. This is the stage when neurosyphilis frequently begins, hence the necessity for spinal fluid investigation, since in untreated and badly treated cases, 25 per cent of fluids will show abnormalities, and even in properly treated primary and secondary syphilis, lymphocytosis, positive globulin and rarely a positive Wassermann and gold curve will be found in about 15 per cent of patients. In the event of abnormalities in the spinal fluid a third or additional series of intravenous injections should be given until the spinal fluid as well as the blood is rendered negative and thereafter another supplementary series. During this time of intensive intravenous therapy by the arsenicals, I have not found it necessary or advisable to employ mercury in any form. At this juncture, however, intensive mercurial treatment should be begun, employing the protiodide pill, clean inunctions or hypodermics of bichloridol, salicylate or gray oil or intravenous injections of cyanide of mercury. Mercurial therapy is persisted in continuously until physiological intolerance is manifest, when the treatment is suspended temporarily and then resumed and held at one-half the former dosage and given in series with periods of rest for two years. The blood examination should be repeated at three to six month intervals the first and second years of treatment and the spinal fluid yearly, in the event of negative blood findings, throughout the patient's life. In the event of blood and spinal fluid abnormalities, intensive treatment with the arsenicals should be resumed. The iodides, so important in tertiary and neurosyphilis, seem to be superfluous in the primary and secondary stages of the disease.

It has long been apparent to me that small or fractional doses of arsphenamin and neoarsphenamin are a mistake for the most efficient treatment of lues, and I prophesied during the recent war that the current practice of small dosage to avoid reactions and keep the men in the firing line was fraught with future peril. Some vindication of the truth of this assertion has already been observed.

It is bound to come. We have heard much of "Wassermann-fast" reactions, but I am happy to state that with the procedure of treatment above detailed I have observed only 2 or 3 cases in many hundreds of patients. I have the conviction that were fractional dosage eliminated from therapy and other drugs withheld until salvarsan or neosalvarsan had accomplished their fullest benefit, administered according to the explicit directions of Ehrlich, fewer severe reactions, fewer immune treponemata pallida and greater and more enduring therapeutic results would be observed.

We have all been surprised and disgusted, if not impressed, in recent years by the great plethora of drugs of the arsenic, mercury, bismuth, silver, antimony, iodine and zinc combinations and brands. A conservative estimate of those marketed numbers not less than sixty. Either much dissatisfaction has been experienced with former antisyphilitic agents or over zealous individuals, laboratories and pharmaceutical firms are crazed with unwarranted impulses to produce something novel for the sake of personal distinction or notoriety or simply for commercial gain. In any event, the pharmaceutical deluge is regrettable, has resulted in much unwarranted experimentation with human life and produced not a few syphilitic derelicts. The most notable of these newer drugs are bismuth, of which potassium and sodium tartrobismuthate, an insoluble salt, is probably the best. It is slower in action than the arsenicals, both clinically and serologically, therefore inferior. It may be on an equal therapeutic footing with mercury, but its toxic complications are more serious than those of mercury. Silver- and neosilver-arsphenamin have received considerable favor in the treatment of neurosyphilis. Compared with the old arsenicals it has the additional disadvantage that argyria has been reported from its use. Sulpharsphenamin or arsenol, less irritating intramuscularly than the original arsphenamins, has not measured up to the fondest hopes of its progenitors. Briefly stated, the therapeutic efficiency of those drugs compared with old salvarsan or neosalvarsan has been disappointing, and their indications for employment exist solely when the former should not be used, namely: Idiosyncrasies against arsenic or mercury, in "Wassermann-fast" cases, possibly in neurosyphilis and in patients where intravenous therapy is inadvisable or impossible.

When shall the patient be permitted to marry and procreate? So much depends upon the duration of infection and condition of the blood at the time treatment was begun, the intensity, character, duration and time elapsed since suspension of that treatment, that each case must be determined on its own merits. Generally speaking, if an opinion must be given, it would be that marriage may be permitted after two years of adequate treatment and an additional year following treatment in which the patient is clinically free of any evidence of lues and the blood and spinal fluid show no abnormalities, although marriage may not be interdicted in a blood

"Wassermann-fast" reaction if the spinal fluid is normal. Procreation should not be sanctioned for two years after marriage and then only in the event of normal blood, spinal fluid and clinical evidence. If the patient be a woman, the restrictions should be more severe. Two years must be allowed to elapse following two years of vigorous and efficient treatment and should pregnancy occur, adequate antisyphilitic treatment must be carried out during that and all subsequent gestations. Antiluetic treatment of the child, even in the absence of clinical signs, is not inadvisable. Just as it is an axiom in latent, tertiary and neurosyphilis, so it is doubtless true that the wise syphilologist will advise his patients in the primary and secondary stage of the disease, at any time exhibiting a positive serological test, to undergo a course of treatment once or twice a year throughout their lives.

The social and economic burden upon the community and taxpayer, so far as human wreckage is concerned incident to syphilitic miscreants and improperly treated syphilis is appalling and difficult of comprehension. In 1916,[1] we pointed out in hospital out-patient services that 44 per cent of 557 syphilities utterly disregarded or ignored their disease, at least primarily, that less than 19 per cent of those patients solicited by personal letters returned to the dispensary and that two-thirds of these were utterly indifferent or refused treatment, stating they "did not care." Accordingly, we concluded at that time that "in view of the fact that less than 12 per cent of our hospital syphilities return for treatment until discharged cured, a problem is presented which urgently demands the coöperation of our civil authorities and health boards for the necessary control and treatment of this disease, not, however, to be realized until all hospitals receiving State aid are compelled to maintain evening dispensaries with paid attendants for the proper treatment and admission, when necessary, of venereal patients." Happily three years later, through the efforts of Dr. Edward Martin, the State Department of Health, through its advisory Board, acting apparently on these suggestions, passed regulations, defining methods by which quarantine could be applied. Since that time 736 lapsed treatment cases were reported in Philadelphia of whom 405 were reclaimed; three premises were placarded and police quarantined until removal to the Philadelphia General Hospital. In the entire Commonwealth approximately 7000 patients have been quarantined. This is surely a step in the right direction for our economic welfare.

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THE PATHOLOGY OF TUBERCULOSIS IN INFANCY, WITH CLINICAL ILLUSTRATIONS.

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Tuberculosis occurring in infancy is even more apt than in older subjects to affect every tissue and organ of the body. The period covered by the term "infancy" includes the first two years of life, but in this paper especial emphasis will be placed on manifestations in the first year. After two years of age, tuberculosis in its pathology, its symptoms and its physical signs enters upon a transitional period leading to the adult type.

The resistance of the infant to infection with the tubercle bacillus is low, and, as a rule, the younger the infant the more generalized does the infection become. The gross and microscopical anatomy of the acute lesions found in young children differ in no essential from those of the acute lesions in older patients. The real difference between tuberculosis in infancy and in later life lies in the fact that practically all the lesions seen at autopsy in children under two years of age are acute. Fibrosis is unknown and calcification is rare. Healing does not occur, and no encapsulated lesions are encountered. Even when only a single tuberculous focus exists in the body of an infant, it is the experience at the Babies' Hospital that the process in that single focus is not a healed one.

Points of Entrance. Tubercle bacilli may enter the infant's body before or at the time of birth through the umbilical vein. After birth the chief portals of entry are the respiratory system and the digestive tract. Occasionally the skin may act as the entrance point for the tubercle bacillus, and the conjunctiva must be considered as a possible portal for a generalized tuberculous infection, since rare cases of primary tuberculous conjunctivitis in small children have been recorded.[1] Primary tuberculous infection by way of the genito-urinary tract is practically unknown in infancy.

I. Tuberculosis Acquired Before or During Birth Through the Umbilical Vein. Tubercle bacilli may be carried to the fetus through the umbilical vein, if the mother suffers from tuberculous endometritis and placentitis, or if she has a bacillemia at the time of the onset of labor without tubercles in the placenta. Tuberculous endometritis and placentitis are rare, though authentic cases are on record (Schmorl and Kockel,[2] Warthin and Cowie[3]). Should tubercle

bacilli be present in the mother's blood at the time of labor, they may enter the torn fetal placental vessels. In either case the bacilli are carried directly to the liver, and then through the inferior vena cava to the right heart and so on to the lungs, before reaching the spleen and other viscera. Consequently infants who die of congenital tuberculosis always show tubercles in the liver and in the lymph nodes draining that organ, and such tubercles are usually more numerous and represent an older stage of the tuberculous process than do those in any other viscus. The lungs in congenital infection are the seat of miliary tubercles without the presence of any single older focus. Congenital tuberculosis is not common, and only two cases have come under the writers' notice.

II. Tuberculosis Acquired after Birth Through the Respiratory Tract. Pirquet estimates that 95 per cent of the tuberculosis of infants is of respiratory origin. Calmette,[4] on the other hand, believes that comparatively few cases originate in that way. In our experience 82 per cent of children under three years of age gave evidence that their tuberculosis had been acquired by inhalation.

Inspired tubercle bacilli are taken up by phagocytes at any point of the respiratory mucosa and carried into the lymph vessels which surround all branches of the bronchial tree, including the alveolar ducts. There are no lymph vessels around the air spaces beyond the alveolar ducts,[5] but the intercellular spaces sooner or later communicate with lymphatics. The bacillus-laden phagocytes may be arrested at any point along the bronchial tree or in the alveolar wall. Again, they may encounter no obstruction until they reach the lymph glands at the hilum, where all lymphatics from the lung and pleura converge. From there the flow is upward to the thoracic duct, into the blood, to the right heart and immediately back to the lungs through the pulmonary artery. Consequently the lungs are doubly exposed; for such inhaled tubercle bacilli as are not arrested in the lungs, nor filtered out on their way through bronchial lymph glands, come back through the pulmonary artery and its capillaries before they reach the systemic circulation and the abdominal viscera.

The Primary Lesion. Wherever inhaled tubercle bacilli first multiply and elaborate their metabolic products, whether in the lungs or in the bronchial nodes, a specific inflammatory reaction results in the formation of tubercles, which then constitute the primary lesion. At autopsy the primary pulmonary lesion in an infant is usually a small cheesy nodule 0.25 to 1 cm. in diameter, surrounded by a zone of miliary tubercles. It may not be apparent on inspection of the lungs at autopsy because of its central situation, but it is palpable as a hard nodule. The lung substance in the immediate neighborhood may be pink in color and well aërated, or there may be a narrow zone of congestion or of consolidation. As a rule, however, the entire lesion is too small to be discovered on

physical examination of the lungs during life. Rarely, two nodules of about the same size may be present in different lobes.

When a lymph gland contains the primary focus, the gland may or may not be enlarged, and the tuberculous lesion may occupy all or only a part of the gland substance. The recent experimental work of Krause[6] has shown that in guinea-pigs gross lesions in the lungs are not indispensable to the appearance of gross lesions in the tracheobronchial nodes. With this our autopsies on young infants agree.

The primary lesion may for a time remain the only one in the body. Since in children under two years of age the tendency is not toward encapsulation and healing, a focus rarely remains single for many months. In a slowly developing tuberculous lesion caused by a non-invasive strain of the tubercle bacillus, which remains latent for a time in one or two foci, small calcareous deposits may appear. It has happened three times that a single tuberculous focus in a bronchial lymph node has been encountered at autopsy, in children seventeen and eighteen months of age. The cause of death was pneumonia in one case, neoplasm of the kidney in another and esophageal stenosis following the ingestion of a solution of lye in the third. In these three instances the tuberculous lesion, though limited in extent and apparently quiescent, was cheesy in character and not encapsulated. The same was true in the case of an infant nine months old who died of bronchopneumonia and showed, at autopsy, a cheesy nodule with a small calcareous center in the upper lobe of the left lung and a cheesy tuberculous area in one bronchial node on the left side.

The primary lesion is found more often on the right side than on the left, and in the upper or middle lobe more often than in the lower.

Type A. Generalized Miliary Tuberculosis Without a Focus Demonstrable by Physical Signs. Tubercle bacilli in an active lesion in the lungs or bronchial lymph nodes must, of necessity, reach the blood stream rapidly, through the thoracic duct. Since the venous blood is sent to the lungs, miliary tubercles form in the lung substance which may remain well aërated, pink in color, and normal in consistency. The spleen is attacked as soon as the bacilli enter the systemic circulation, and bacilli not filtered out by the spleen go on to the liver and other organs. Cases of this kind are common in young infants, who then die of a more or less generalized miliary tuberculosis, a bacillemia. The first successful culture of tubercle bacilli from human blood was obtained by Faber[7] in a postmortem case at the Babies' Hospital.

When the primary focus in the lungs cannot be demonstrated by physical signs—percussion, auscultation, etc.—the case belongs to the clinical type designated as general miliary tuberculosis without a focus demonstrable by physical signs, which includes

only a small proportion of the cases of tuberculosis in infancy. The diagnosis is usually not made before death.

CASE REPORTS. Illustrative case histories have been chosen of patients who have died in the Babies' Hospital and upon whom autopsies have been made.

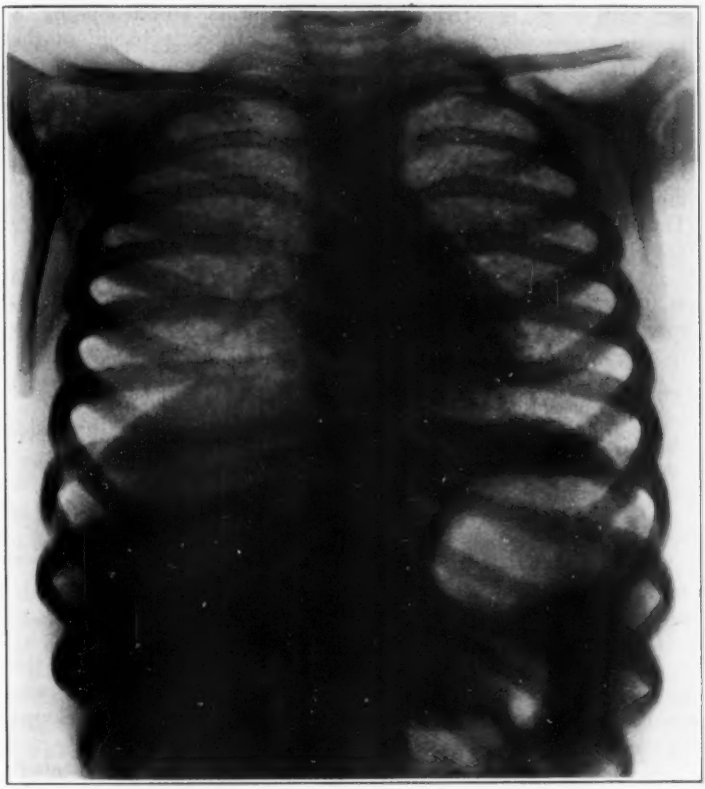

FIG. 1.—Type A. Roentgenogram of military tuberculosis of the lungs without any demonstrable focus. Note the profusely and evenly scattered tubercles in both lungs.

CASE I. L. R., aged seven months.

Chief Complaint. Cough, five weeks; diarrhea, two weeks.

Family History. Mother coughs, has night sweats and has lost weight rapidly since the baby was born; 3 other healthy children.

Birth History. Normal delivery; weight 7 pounds.

Feeding History. Still being nursed; has never been weighed since birth, but was a plump baby.

Present Illness. Began five weeks ago with a "cold" which persisted; cough and some fever, with rapid loss of weight. For the past two weeks has been having four or five loose green stools each day. Appetite poor.

Physical examination showed a moderately rachitic, poorly nourished child with enlarged spleen and liver, many fine rales throughout both lungs, negative findings in the urine, no adenopathy, a positive tuberculin skin reaction and no tubercle bacilli in the sputum.

Diagnosis. Rachitis; miliary tuberculosis of the lungs.

Subsequent Course. During the six days preceding his death, the child showed steady loss of weight with slightly irregular fever. He became drowsy and developed general rigidity. The spinal fluid was normal; it contained 15 cells but no tubercle bacilli. The blood count showed 9,000 leukocytes with 45 per cent polymorphonuclears.

At *autopsy* the anatomical diagnosis was acute miliary tuberculosis of the tracheobronchial lymph nodes, lungs, liver, spleen, kidneys; caseous tuberculous foci in lungs and tracheobronchial lymph nodes.

Case II. C. E., aged five months.

Chief Complaint. Vomiting; loss of weight for two months.

Family History. Mother has tuberculosis; 1 other healthy child.

Birth History. Normal delivery; weight 8 pounds.

Feeding History. Never nursed; formula not know.

Present Illness. Baby has been at preventorium for past month; sent there as "sick," without details.

Physical examination showed an emaciated infant with a positive tuberculin skin test, but without abnormal signs in the lungs and no tubercle bacilli in the sputum; no adenopathy.

Diagnosis. Marasmus.

Subsequent Course. During the five weeks that he was in the hospital the gain in weight was small. The temperature was subnormal most of the time. No abnormal physical signs developed in the chest.

At *autopsy* the anatomical diagnosis was: Acute miliary tuberculosis of lungs, liver, spleen and heart; caseous tuberculous foci in lungs and tracheobronchial lymph nodes.

Discussion. Chief Complaint. The chief complaint in Case II defines it as a disturbance of digestion; in Case I as a combination of disease of the digestive and of the respiratory tract. The chief complaint frequently gives no clue to the fundamental disturbance. A combination of persistent cough and loss of weight with some fever, should make one suspicious of miliary tuberculosis.

Family History. If an infant has been exposed to individuals with active tuberculosis, one is justified in being apprehensive

that he has picked up the infection. In both illustrative cases there is a clear history of exposure.

Feeding History. In the early period of infection the child may take his food well. As a rule, as the disease progresses, the nutrition retrogresses.

Previous Illness. Case II had had no acute illness previous to admission. Case I had had a cold which persisted, and also loose stools. The absence of a history of previous illness in these patients is common.

General Appearance. The notes on both infants mentioned their undernutrition. Case II did not appear acutely ill; Case I did. This confusing evidence is purposely emphasized to show how difficult it is to recognize a miliary tuberculosis from the general appearance of the infant. The presence of cyanosis without adequate reason is helpful, directing the attention to tuberculosis.

Chest. The physical examination of Case II showed nothing abnormal in the lungs. An examination of Case I showed general bronchitis. It is impossible to elicit abnormal physical signs from a lung containing only miliary tubercles. The presence of an associated bronchitis which persists with proper treatment, may suggest a general miliary tuberculosis. The roentgen-ray furnishes the only help to a demonstration of miliary tubercles in the lungs. Multiple small abscesses in the lungs may, though rarely, give a similar roentgenogram, and lead to confusion in the interpretation of the plate. Multiple peribronchial pneumonic areas also give a roentgen-ray picture like miliary tuberculosis; they are frequent in cases of influenzal pneumonia.

Abdomen. The liver is usually enlarged in general miliary tuberculosis. However, the edge of the liver is felt in so many infants that little help is offered by this sign. The enlargement of the spleen is frequent. This physical sign is emphasized.

Lymph Nodes. In both infants there were no abnormal enlargements. In infants under a year of age tuberculosis of the cervical lymph nodes is not common.

The Course of the Disease Observed by the Physician. Fever. The temperature of Case II was subnormal through her five weeks stay in the hospital; Case I's temperature fluctuated between 99° and 102° F., one day reaching 103° F. This fluctuating temperature is more common than the subnormal type. Reference is made to the latter form to guard against dismissing general miliary tuberculosis because of a subnormal temperature.

Respiration. There is no significant variation in the breathing.

Vomiting. Apparently there is no significant association between vomiting and a general miliary tuberculosis, unless there is a focal lesion in the brain.

Bowels. The stools are as likely as not to be normal, and this is true even if there are ulcers in the intestines.

Special Tests. The tuberculin skin test is a valuable aid in determining the presence or absence of general miliary tuberculosis of the type under consideration. A positive reaction in children under two years of age means a tuberculous infection and is significant. The test may be negative in tuberculous infants who are moribund or who are in a condition of extremely low resistance. It is urged that the test be made more than once if the first attempt is negative. The intradermal test is more sensitive than the Pirquet test.

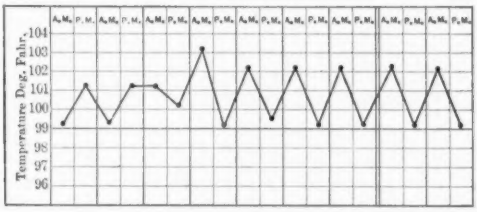

Chart I.—Case I, "L. R."

Laboratory Examination. *Sputum:* In the great majority of infants who have a general miliary tuberculosis without demonstrable focus, tubercle bacilli are not found in the sputum. *Blood Count:* The white cells may be normal in number or they may be increased to 20,000 or 30,000. It is, however, unusual to see the white cells above normal in a general miliary tuberculosis, unless there is a secondary bronchopneumonia or bronchitis. It may be stated that the blood count is of little value.

Prognosis. Fatal in every case.

Comment. Attention is called to the finding of caseation of the lungs at autopsy in both cases. These caseous foci were too small to be demonstrated by the usual method of physical examination.

Type B. Generalized Miliary Tuberculosis with a Focus Demonstrable by Physical Signs—Bronchopneumonia, Simple and Cheesy. A child who has a miliary tuberculosis sometimes acquires a non-tuberculous bronchopneumonia which may cause his death. At autopsy the lungs are swollen, heavy, red, and show an extensive consolidation of bronchopneumonia in the greater part of one or more lobes, with gray or yellow tubercles in large numbers scattered over both lungs.

On the other hand, cheesy bronchopneumonia may develop: the primary pulmonary focus spreads locally, a wider zone of tubercles forms around it and the alveoli of the surrounding lobules become filled with exudate which rapidly undergoes coagulation necrosis. Small areas of cheesy bronchopneumonia result and by

their coalescence more or less of one lobe may become involved. Often the earliest cheesy areas develop about small bronchi and give a characteristic clover-leaf effect to the lesion. The lung substance between the cheesy areas may remain pink and aërated for a time, but soon becomes dark red and solid. If softening of a cheesy area occurs a cavity results. The cavity usually opens into a bronchus. It may be only 0.5 cm. in diameter or it may involve the greater part of a lobe. Pulmonary hemorrhage is very rare in young children, although bloodvessels of appreciable size may be seen in the walls of a cavity.

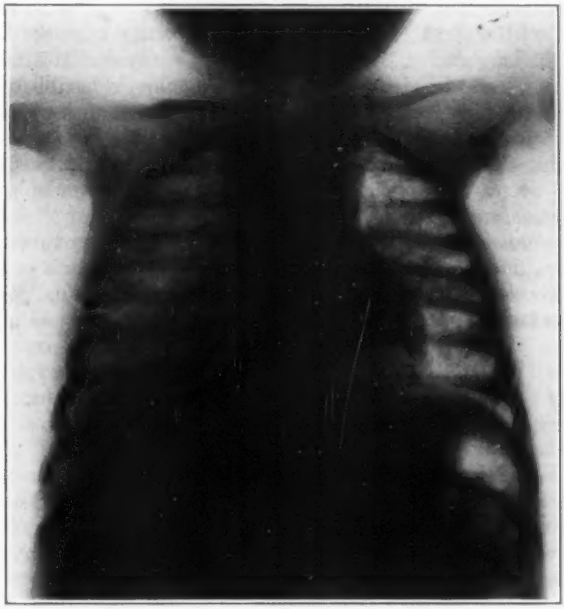

FIG. 2.—Type B. Roentgenogram of tuberculous pneumonia in right lower lobe with small cavity in center, cheesy pneumonia with smaller cavity in left lower lobe, and miliary tubercles over both lobes.

In cheesy bronchopneumonia many tubercle bacilli are present in the sputum. The swallowing of tubercle-bacillus-laden sputum may lead to the formation of ulcers in the small and large intestines. The ulcers may be present in the duodenum, and may extend to the rectum.

The bronchial lymph nodes at this stages have usually become enlarged to one or more times their original size, with extensive areas of cheesy degeneration and softening due to suppuration. Many tubercle bacilli are present in such softened nodes.

CASE III. R. G., aged six months.

Chief Complaint. Cough, two months; fever, one day.

Family History. No tuberculosis.

Birth History. Normal delivery; weight 8 pounds.

Feeding History. Nursed for fifteen days, then milk formula; did well.

Previous Illness. Baby had been at hospital with bronchopneumonia three weeks ago, and had only done fairly well since.

Present Illness. Baby has had a slight cold for over two months; no vomiting; seems hungry; fever began this morning, amount not known; stools two or three a day, fair; baby gaining very slowly.

Physical examination showed a poorly nourished, fretful, rachitic infant, with slight dyspnea, diminished resonance over the base of the right lung and in the right axilla, and many moist rales, more numerous over the right lung behind; no tubercle bacilli found in the sputum.

Provisional Diagnosis: Bronchopneumonia.

During the next three weeks, the pulmonary signs persisted, the weight decreased, and death occurred after two days of marked prostration and cyanosis.

The *anatomical diagnosis* was: Rickets; acute miliary tuberculosis of lungs, liver, spleen, kidneys, mesenteric lymph nodes; caseation of tracheobronchial lymph nodes and lungs; fibrinous pleurisy; acute catarrhal bronchitis.

CASE IV. M. K., aged thirteen months.

Chief Complaint. Cough; loss of weight for five months.

Family History. Mother has tuberculosis.

Birth History. Normal delivery; weight 9 pounds.

Feeding History. Nursed for three months; milk from Board of Health Station for two months; condensed milk for eight months. For last six weeks has also had oatmeal, zwieback, etc.

Previous Illness. Seemed perfectly well until five weeks ago.

Present Illness. Began slowly with cough and stationary weight; during the last few weeks has been losing weight, when three months old, weighed 13 pounds; has slight fever occasionally; coughs mostly at night and generally very loose; three weeks ago spat up a little blood.

Bowels. Regular; stools good.

Physical examination showed an emaciated white male child who appeared chronically ill, weak and prostrated, with rapid respirations and some dyspnea, but no cyanosis. Tuberculin skin test was positive and tubercle bacilli were found in the sputum.

During the three weeks in the hospital he lost weight, the pulmonary signs remained unchanged and an eruption of tuberculides resembling chicken-pox, developed. He became progressively weaker until he died.

Anatomical Diagnosis. Tuberculids of the skin; acute miliary tuberculosis of lungs, liver, spleen, peritoneum, kidneys; caseation of lungs, tracheobronchial, mesenteric, cervical lymph nodes; cavitation of lung; tuberculous pleurisy; tuberculous enteritis; fatty and congested liver.

Discussion. Chief Complaint. A review of a number of case histories of this type of tuberculosis shows that cough, fever, and loss of weight, rapid respiration and occasional vomiting appear in the chief complaint in different combinations.

Family History. It is probable that in a large majority of tuberculous infants a history of exposure to tuberculosis could be traced if a searching investigation were carried out.

Previous Illness. It is rather striking that no history of previous illness can be obtained in a considerable proportion of infants with tuberculous bronchopneumonia. There is no doubt that a predisposition to tuberculosis is determined by an attack of measles or whooping-cough. Persistent cough, fever, and loss of weight following these diseases may reasonably make one suspicious of tuberculous infection.

Present Illness. This is summarized in the chief complaint. Case IV gives a history of spitting blood, which is not usual in infants. This point is especially emphasized.

Chest. It is impossible, unless there are signs of a cavity, to differentiate tuberculous bronchopneumonia from a non-tuberculous bronchopneumonia by physical signs. The determination of the tuberculous character of the lesion must be made by an examination of the sputum, by a skin test, by a history of exposure, and by the duration of the disease. A tuberculous bronchopneumonia is likely to have a longer duration than a non-tuberculous bronchopneumonia. It must not be forgotten that a simple bronchopneumonia is often superimposed on a pulmonary tuberculosis and adds confusion to the diagnosis.

Lymph Nodes. It is not common to find the superficial lymph nodes involved in tuberculous bronchopneumonia, but roentgen-ray examination of the chest will show an enlargement of the mediastinal nodes in the majority of cases.

Skin. Tuberculids of the skin often look like the eruption of chicken-pox and are easily mistaken for it. Tuberculids in infants establish the diagnosis of a general tuberculosis of which tuberculous bronchopneumonia may be a focal manifestation.

The Course of the Disease Observed by the Physician. Fever. Case III's temperature chart may be studied as representing a composite of the different types of temperature found in tuberculous bronchopneumonia. Probably the most usual type is that represented in the first week—a remittent fever. A second type is represented in the complete chart—a combination of remittent temperature, and normal and subnormal temperatures; and a third

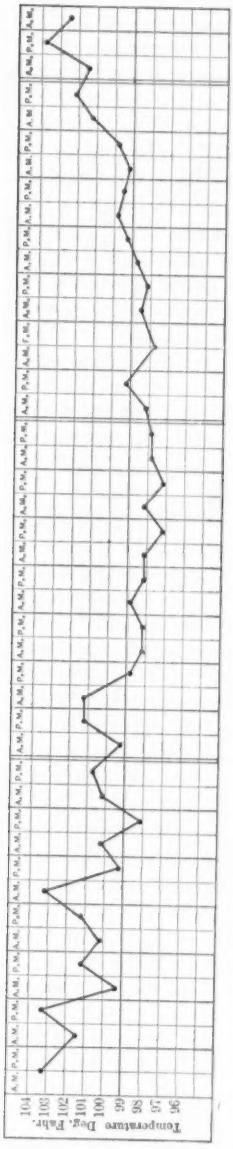

CHART II.—Case III. "R. G."

type is that represented by the subnormal phase of the temperature. Tuberculous bronchopneumonia in infants may run its course with a subnormal temperature, though this is not usual.

Respiration. The breathing in tuberculous bronchopneumonia is frequently more rapid than would be accounted for by the physical signs.

Nutrition. In an infant, carefully fed, a steady loss of weight in association with physical signs of bronchopenumonia is one of the most important evidences of the tuberculous nature of the disease.

Special Tests. If an infant has a demonstrable focus in the lungs the likelihood of finding tubercle bacilli in the sputum is much greater than in Type A, where there is no demonstrable focus. It is essential that repeated examinations be made.

Blood Count. The total leukocyte count is more often over than below 10,000 and the polymorphonuclears are more often over than below 50 per cent of the white cells. This high leukocyte count may be accounted for in many cases by a complicating bronchopneumonia.

Comment. Cavitation is frequently present in tuberculous bronchopneumonia, even in young infants, especially if there is an extensive involvement of the lungs. The detection of a cavity is an important contribution to the diagnosis.

There may be a tuberculous ulceration of the intestines without symptoms or physical signs referable to the intestinal tract. It was so with Case IV.

Prognosis. Probably every infant dies who has a tuberculous bronchopneumonia as a part of a general miliary tuberculosis. There has been no case of tuberculous bronchopneumonia at the Babies' Hospital without a dissemination of tubercle bacilli in other organs. The younger the infant, the less likelihood there is for a tuberculous process to confine itself to the lungs.

Type C. General Miliary Tuberculosis with Focal Lesions in the Meninges—Tuberculous Meningitis. Tuberculous meningitis terminates about 40 per cent of all cases of general miliary tuberculosis in children under two years of age. It occurs in a much higher percentage of cases which originate by inhalation of the tubercle bacilli than by ingestion. At the Babies' Hospital the bovine type of tubercle bacillus was found in 3 cases of tuberculous meningitis following a primary lesion in the digestive tract. In the great majority of cases, however, it is the human type of bacillus which is found in the spinal fluid.

At autopsy miliary tubercles are present in smaller or larger numbers along the vessels of the pia mater over all the surfaces of the brain and cord. Often they are also found in the choroid plexus and over the floor of the lateral ventricles. An exudate of serum and fibrin is usually limited to the base of the brain, where it infiltrates the pia in the interpeduncular space and over the isles

of Riel. It may spread to both surfaces of the cerebellum. Rarely such an exudate extends along the vessels over the surface of the cerebral hemispheres. The ventricles as well as the Sylvian aqueduct may be more or less dilated, following closure of the foramina of Luschka and Magendie by inflammatory exudate.

Tuberculous masses 0.5 to 2 cm. in diameter are encountered in the substance of the cerebrum or of the cerebellum in about 2 per cent of cases of tuberculous meningitis in young children. These lesions have a cheesy center which may undergo softening. The pia mater over and near them is usually studded with tubercles.

In rare cases tuberculous meningitis may be complicated by the presence of the meningococcus, the Pfeiffer bacillus, the pneumococcus or the streptococcus. All these bacteria cause a purulent inflammation of the meninges which obscures both the clinical and the pathological picture, making a correct diagnosis difficult during life. No case of recovery from tuberculous meningitis has ever been observed at the Babies' Hospital.

CASE V. D. B., aged eight months.

Chief Complaint. Drowsiness, one week; stupor, three days; slight cough, one month.

Family History. Tenth child; father tuberculous.

Birth History. Normal delivery; small baby.

Feeding History. Nursed for three months, then fed condensed milk; gained well.

Previous Illness. None.

Present Illness. Has had a slight cough for a month; for the past week has been drowsy, but could be roused; for three days baby has been in stupor; no convulsions; very constipated; appetite poor.

Examination showed a well nourished infant, drowsy, with bulging fontanelle, slow respirations, palpable liver and spleen, marked tache, hyperactive knee jerks and double Babinski.

The child became comatose and died the day after admission.

Anatomical Diagnosis: Acute miliary tuberculosis of brain, meninges, vocal cords, lungs, liver, spleen, kidneys; tuberculous caseation of tracheobronchial lymph nodes.

CASE VI. J. C., aged nineteen months.

Chief Complaint. Constipation, three weeks; drowsiness, three days; convulsions, twelve hours.

Family History. No tuberculosis; 1 other child well; 1 died of pneumonia four months ago.

Birth History. One of twins; normal delivery; weight 5½ pounds.

Feeding History. Bottle-fed since birth; at present getting whole milk and farina.

Present Illness. Except for constipation was well until two weeks ago when he became irritable; no vomiting; had slight fever; refused

food; three days ago became drowsy; has been getting worse and is never awake at present; had general convulsion twelve hours ago, lasting fifteen minutes; face has twitched since convulsion; no cough.

Physical examination shows a poorly nourished negro male child, acutely ill, with spasticity of the whole right side, tonic spasms of the arm, leg, right face and neck, a fine nystagmus and an irregular strabismus, irregular respiration, few rales and diminished resonance over apices. Babinski, Kernig and tuberculin skin test positive.

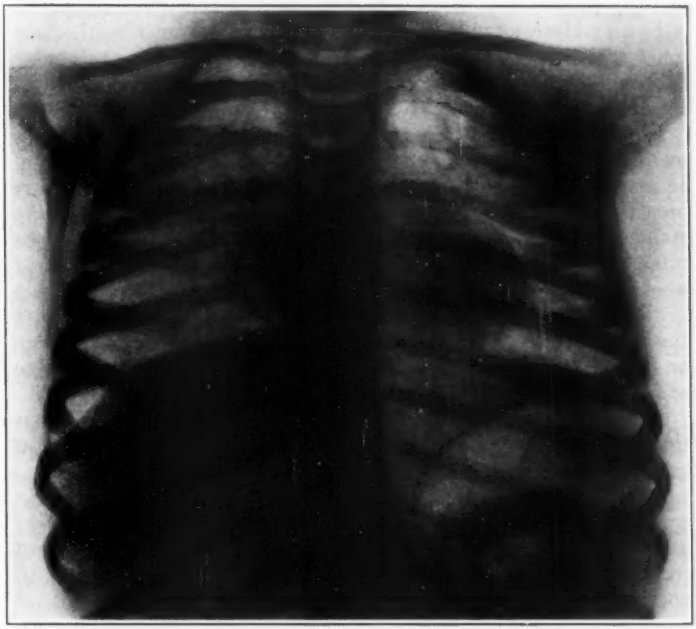

FIG. 3.—Type C. Roentgenogram of miliary tuberculosis in both lungs; cheesy area in right upper lobe. Death from tuberculous meningitis.

Provisional Diagnosis: Tuberculous meningitis; pulmonary tuberculosis.

During five days in the hospital, he had frequent convulsions, refused food, and became progressively more drowsy.

Anatomical Diagnosis. Acute miliary tuberculosis of meninges, lungs, pleura, liver, spleen; tuberculous caseation of tracheo-bronchial and mesenteric nodes; tuberculous enteritis.

DISCUSSION. CHIEF COMPLAINT. Practically every patient with tuberculous meningitis is admitted to the hospital with a history of drowsiness or stupor as one of the symptoms in the chief complaint. The combination of symptoms which point most signifi-

cantly to tuberculous meningitis is drowsiness, irritability and vomiting. The reason for the comparative infrequency of convulsions in the early stages of the disease is easily explained by the fact that the lesion is located with greatest intensity at the base of the brain. It is impossible to differentiate the drowsiness of tuberculous meningitis from that of encephalitis lethargica. If, however, there are associated with it symptoms of irritability it is more likely to be tuberculous meningitis.

Duration. The duration of the disease from onset to death, at this period of life, is at the longest, three to four weeks.

Family History. In most cases of tuberculous meningitis there must have been an exposure to an individual who has an active tuberculosis, since meningitis due to the bovine tubercle bacillus is comparatively rare.

Feeding History. There is a curious idea that tuberculous meningitis is more commonly seen in poorly nourished children. It is seen as often in the well nourished. Many of the infants are breast fed. Constipation and occasional vomiting are almost constant symptoms. They may precede the onset of symptoms definitely referable to the central nervous system by a few days or weeks, but more often they appear at the time of the definite onset of the meningitis. The nutrition fails rapidly during the course of the disease. Vomiting, as a rule, is at infrequent intervals and may be absent. If the course of the disease is prolonged to two, three or four weeks the emaciation becomes extreme.

Previous Illness. The fact which should be emphasized is that an infant may have been perfectly well up to the onset of a tuberculous meningitis.

General Appearance. Drowsiness is perhaps the most common condition early in the disease. Signs of cerebral irritation appear as a rule in the first week. The infant may have one or more general convulsions; localized spasms are common; one side of the face, one arm, or one leg may twitch; the eyes are in bizarre forms of strabismus; nystagmus comes and goes; occasionally there may be periods in which the head and lower extremities are bent back; opisthotonos is often followed by relaxation. The variability in the location and duration of muscular spasms is almost characteristic of tuberculous meningitis. Constant rigidity of the neck is more characteristic of cerebrospinal meningitis than of tuberculous meningitis.

Chest. There may be no physical signs, or there may be signs of a tuberculous bronchopneumonia.

Extremities. The infant will often hold the legs so stiffly that it is difficult to flex them. At other times they will be flaccid. A variability of stiffness and relaxation of the lower extremities is common.

Reflexes. The knee-jerks are at times increased, at times normal or at times absent. Kernig's sign is usually present at some time in the course of the disease. The same variability is seen in the Babinski sign. A tache is present in practically every case.

Course of the Disease Observed by the Physician. The disease may run its course with a normal or a subnormal temperature. The more frequent type is a remittent fever. Irregularity in the rate and the depth of breathing is constantly observed. The heart action likewise shows irregularity in force and frequency.

Spinal Fluid. The presence of a tuberculous meningitis is determined by examination of the spinal fluid for tubercle bacilli. They can be found in 95 per cent of all cases. This statement is made on the supposition of careful and prolonged search. The fluid is clear in most instance, but sometimes it is slightly turbid. If the fluid is allowed to stand in a test tube, a veil-like film forms. It gives the appearance of being suspended from the surface of the fluid. Since the fibrin entangles the bacilli, it is by spreading the film on a slide and staining it that the organisms are found. As a rule, the fluid is under increased pressure. The number of cells is increased. (Ten to 15 cells per cm. may be regarded as representing the maximum normal count.) The lymphocytes usually represent over 80 per cent of the cells. Rarely, and toward the end of the disease, the polymorphonuclear cells are more numerous than the lymphocytes. The test for globulin is positive.

Comment. It would be possible to select enough autopsy reports to demonstrate that miliary tubercles were present in practically every organ of the body. Tuberculous meninigtis in infancy is part of a general miliary tuberculosis, dissemination of the tubercle bacilli being by way of the blood stream. This will explain the high death rate in early life. Rarely, and in children over two years of age, the lungs, liver, and spleen may escape, and the cerebrospinal meninges may be attacked first by the tubercle bacilli which have entered the blood stream from a tuberculous focus in a bronchial lymph node. We have seen two cases of this kind in children over two years of age.

Prognosis. Probably fatal in every case in infants under two years.

Treatment. None.

III. Tuberculosis Acquired After Birth Through the Digestive Tract. Tubercle bacilli may enter the mouth of a child with food, or they may be carried there by the child's fingers, toys, or utensils, or by the fingers of his attendants. The results of such ingestion vary with the course taken by the bacilli, and the point at which they are arrested.

(*a*.) The tonsils may arrest the bacilli, become the seat of tuberculous inflammation and discharge tubercle bacilli into the cervical lymph nodes which drain the tonsil; or the bacilli may reach these

nodes without the development of a tonsillar lesion. General tuberculosis from such a source is of slow development, and of rare occurrence in children under two years of age. We have not met such a case in an infant.

(*b.*) When tubercle bacilli are swallowed, they usually pass through the stomach with the food into the intestines, where they are carried by phagocytes into the lymphatics. They may leave the intestinal wall without starting any lesion there, but the mesenteric lymph nodes will filter some of them from the lymph stream and become the seat of tuberculous inflammation. The process is similar to that which takes place in the respiratory tract. If the tubercle bacilli are few and of low invasive power, one node may be able to filter them all, and then if no more bacilli are ingested, the lesion in the node may remain inactive for months and even become calcified. But in children under two years of age completely healed tuberculous lesions have not been encountered by us, and sooner or later bacilli in the lymph node are stimulated to multiply, and, entering the lymph stream, reach the general circulation, to localize in any organ prepared for them. The youngest child in whom we have encountered tuberculosis limited to one mesenteric node was two years and ten months old.

(*c.*) Tubercle bacilli may pass through the intestinal wall and form tubercles in several mesenteric glands and in the peritoneum, causing extensive tuberculous peritonitis and finally more or less generalized tuberculosis.

(*d.*) Finally, swallowed tubercle bacilli may localize in the lymph follicles of the intestinal wall at any level, and form typical ulcers. Large numbers of bacilli may enter the lymphatic vessels from these ulcers and cause typical lesions in the mesenteric nodes and the peritoneum. Eventually the bacilli reach the celiac plexus, the thoracic duct and the general circulation.

In cases of primary tuberculosis of the digestive tract, with or without peritonitis, the lungs and tracheobronchial lymph nodes may be entirely free from tuberculous lesions. But if the child lives long enough, miliary tuberculosis in the lungs and their lymph nodes results. The age of the lesions above and below the diaphragm is distinctly different, however.

The stomach is infrequently the seat of tuberculous lesions. Only in a very generalized tuberculosis are typical ulcers formed on the gastric mucosa. They are usually small, 1 to 3 mm. in diameter, one or two in number, along the greater curvature or in the posterior wall in the pyloric half of the stomach. They cause no clinical symptoms. The ulcers involve all the coats of the organ, as in the intestines.

Tuberculous Peritonitis. Tuberculous peritonitis is found less often in young infants than in children over two years of age. It is almost

invariably the result of primary tuberculous infection of the digestive tract, and the mesenteric lymph nodes are practically always the seat of tuberculosis, although the intestines may be quite free. In most cases, however, there are extensive tuberculous ulcers in the small intestine. The mesenteric nodes may be markedly enlarged, sometimes forming masses 4 to 6 cm. in diameter.

DIAGNOSIS. The usual history in these children is that: (1) The abdomen has gradually increased in size; (2) there is discomfort and pain in the abdomen; (3) there is slight intermittent fever; and (4) there is constipation. The enlargement of the abdomen must be distinguished from that seen in chronic intestinal indigestion. An important difference is that in the latter condition the size of the abdomen varies at different times of the day. It is usually large after meals and almost always larger at night than in the morning. In tuberculous peritonitis the circumference of the abdomen is not so likely to vary in size. To determine this point, it is necessary to measure the abdomen at different times of the day. If the abdomen is carefully palpated one finds masses in tuberculous peritonitis. Perhaps the most common location of these tumors is above the navel extending across the abdomen. This respresents a rolled up omentum in a mass of tuberculous adhesions. Such masses are not found in chronic intestinal indigestion. If in this condition there are fecal accumulations which might be taken for tuberculous masses, a cathartic will get rid of them.

Tuberculous peritonitis (in very young children) associated with a large quantity of fluid in the abdomen is not so common as is the fibrinous form.

The tuberculin skin test should be made as an aid in interpreting the condition. After two years of age a positive reaction is not so significant as in early infancy. It cannot, however, be disregarded.

In the case of a very generalized tuberculosis following infection by inhalation, especially in young infants, the peritoneum may be invaded, as any other organ may be, and no special symptoms result.

TREATMENT. Surgical treatment has proved most unsatisfactory. A gradually increasing time exposure to the sun's rays with proper food, and plenty of fresh air, offer the best hope of improvement. It is important to begin with an exposure of ten to fifteen minutes and to increase by five to ten minutes each day up to several hours a day. The outlook is better if the skin of the abdomen tans. This treatment can be carried out at home.

IV. Tuberculosis Acquired After Birth Through the Skin. Any simple lesion or surgical wound of the skin may become the primary focus from which a generalized tuberculosis may develop. In young infants the wound of a circumcision operation has occasionally proved such a focus, feeding bacilli to the neighboring inguinal lymph nodes, causing typical lesions. The lesion in the wound and

lymph nodes constantly feeds bacilli to the lymph stream and consequently to the blood. Dr. Holt[8] has recorded such a case.

General tuberculosis has been reported as resulting from the infection of a small skin lesion. So in Sheltema's[9] case, a tuberculous father cared for his child who had a small sore on the forehead.

Type of Tubercle Bacillus Infection. The human type of tubercle bacillus is by far the most frequent cause of tuberculous infection in young children. Park and Krumwiede [10] estimate that bovine infection causes less than 10 per cent of the total deaths from tuberculosis in young children. In this country, the proportion is lower than it is abroad, especially in Great Britain. An unselected series of fatal cases from the Babies' Hospital was studied by Park and Krumwiede, who found 6.33 per cent due to bovine type of tubercle bacillus. In England, Cobett[11] found that 33 per cent of all the children under five years who die from tuberculosis are infected with bovine bacilli. This type of tubercle bacillus causes the majority of infections of the cervical lymph nodes, of the alimentary tract and of the peritoneum, while the human type causes pulmonary tuberculosis and the great majority of cases of meningitis. Only about 4 per cent of tuberculous meningitis is due to the bovine bacillus. Mixed infection with human and bovine bacilli may take place, the pulmonary lesions in such cases being due to the human type and the abdominal lesions to the bovine type of bacilli. Finally, both types have been found in the bronchial nodes.

Significance of Positive Tuberculin Skin Tests. 1. *In infants under six months without symptoms or physical signs of tuberculosis:* The statement may be ventured that over 75 per cent of such infants will develop tuberculosis within the first year of life. This is tantamount to saying that the infant will die of tuberculosis within one year.

2. *In infants between six and twelve months without symptoms or physical signs of tuberculosis:* One is warranted in saying that 50 per cent or more will develop tuberculosis within a year; or in other words, they will die of it within that time.

3. *In infants between one and two years without symptoms or physical signs of tuberculosis:* Between 25 and 50 per cent will develop the disease. There is a better chance of their escaping a fatal outcome.

General Conclusions. The seriousness of tuberculosis in infancy is evident. If one realizes that a majority of the infants under a year of age with tuberculosis are killed by it, regardless of treatment, one may well ask, what is to be done? The only answer to this question is that every infant must be kept away from those who have tuberculosis. The only treatment for tuberculous infants is preventive; that means absolute isolation from anyone who has tuberculosis. This obviously is best accomplished by the isolation of the tuberculous individual.

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COMPARISON OF THE BLOOD-PLATELET COUNT IN SPLENIC ARTERIAL AND VENOUS BLOOD.*

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Since Kaznelson[7] recommended splenectomy for cases of thrombocytopenic hemorrhagic purpura, surgical treatment has been followed in 16 cases with brilliant results (Giffin).[2] Many theories have been advanced in an attempt to explain why splenectomy has such a desirable effect, but a satisfactory explanation of the phenomenon is lacking. The outstanding findings in thrombocytopenic hemorrhagic purpura are prolonged bleeding-time, irretractability of the blood clot, and a marked reduction in the number of the blood platelets in the peripheral capillary circulation. Prolonged bleeding-time and non-retracted clot probably depend largely on the insufficient number of blood platelets present (100,000 or less) (Gram).[5] It is, therefore, of prime importance to determine, if possible, the cause of the reduced number of blood platelets.

As platelet counts vary within wide limits, partly because of technic, even in persons suffering from acute exacerbations of purpura, and as splenectomy is followed by a marked and almost immediate rise in the platelets, it is reasonable to assume that there is no lack of production in this disease, but rather an increased destruction of this important blood corpuscle. It is most commonly believed that hemorrhagic purpura is the result of an infectious

* Work done in the Department of Experimental Surgery and Pathology and Section on Medicine, under the direction of Dr. H. Z. Giffin.

process, with the production of some toxic material which rapidly destroys blood platelets. The toxin affecting these changes is perhaps a secondary substance, the production of which is initiated by the pathological process, possibly some abortive substance originally designed to protect (Giffin and Holloway).[3] It is possible that this process is closely linked with protein intoxication and anaphylaxis (Glanzmann).[4] As splenectomy has been followed by such a remarkable rise in blood platelets, together with a disappearance of clinical symptoms, it is to be assumed that the pathological process which leads to the excessive destruction of platelets has its basis in the lymph glands and hemolymph glands, Kupffer cells of the liver, and probably in other parts of the reticulo-endothelial apparatus, of which the spleen is a major member.

In 2 cases in which operation was performed for hemorrhagic purpura, it is reported that the blood from the splenic vein contained fewer platelets than blood from the peripheral circulation. In the case operated on by Cori,[1] the counts were 1200 in the splenic vein and 4000 in the peripheral vein. In the case in which operation was performed at the Mayo Clinic, the splenic vein showed a count to 40,000 as compared with 80,000 in the capillary circulation (Giffin).[2] These counts, however, are so low that they cannot alone be a basis for conclusions. It is, however, impossible to judge how satisfactorily these observations were carried out. With these findings in mind, we have undertaken to ascertain: (1) Whether the platelet count of blood from the splenic vein differed from that of the splenic artery; and (2) whether there was any difference in counts made of the blood from the peripheral veins and peripheral arteries in normal dogs.

The comparison of red blood cells in the splenic vein and the splenic artery has been made by Krumbhaar and Musser,[8] and others. Their figures for red and white blood cells, differential counts, and total hemoglobin show that the blood of the splenic vein does not differ greatly from that of the artery, and that all variations were "within the limit of error inherent in the methods of blood examination."

Method of Experimentation. Active and well nourished dogs were selected, but 1 of them (Experiment 2) had distemper at the time the counts were made. Ether was used as an anesthetic. The spleen was gently drawn through the abdominal wound and wrapped in pads moistened with warm sodium chloride solution. Great care was exercised to disturb the organ or vessels as little as possible, bearing in mind that congestion of the spleen causes greatly increased content of blood from the splenic vein.[6, 9] With an aneurysm needle the splenic vein and artery were carefully isolated and dissected, the fields being kept very dry. Blood from the vein was taken first. With a small Graefe knife a venipuncture was made, which afforded an abundant supply of blood coming from

the spleen. Several samples were thus secured in Thoma counting pipettes, fresh sodium citrate solution being used as a diluent. The vein was then clamped across the bleeding point without obstruction to the circulation. Similar methods afforded samples from the arterial circulation. That we might control our experiments as well as possible, we secured at the same time samples of blood from the splenic vein and artery for counting red blood cells and white blood cells. In Experiments 5 to 10, inclusive, a diluting solution consisting of 3.8 per cent sodium citrate and 0.2 per cent formaldehyde (modification of method devised by Rees and Ecker)[10] was employed, because of the claim that the presence of formaldehyde prevents the disintegration of cells and the formation of the so-called Arnold bodies. In the other experiments a 2 per cent solution of sodium citrate was used, and this has been adopted routinely. All counts were made on Levy chambers. Each sample of blood was counted by two or three persons, thus securing from four to six counts on the samples taken. Similar methods were employed in securing counts from the jugular vein, carotid artery and femoral vessels. By comparing our findings in specimens of blood taken from areas supplying various types of tissues, we were enabled to control our results even more closely than would be possible by comparing the erythrocyte and leukocyte counts in the splenic circulation. Furthermore, the work was done by a trained unit. We feel assured, therefore, that our range of technical error was reduced to a minimum. Even with such care, there appeared at times rather marked variations in the individual platelet counts. It is possible that these were due to variations in platelet content of the various blood samples, which were taken over periods of several minutes. However, we quite agree with other observers that the counting of blood platelets is somewhat unsatisfactory, and that rather generous limits should be allowed for error. Indeed, variations in counts ranging as high as 100,000 are not uncommon. The relationship between the counts of arterial as compared with venous blood was usually constant. (Table I). Tables I and II show the results of our experiments on 20 dogs. Eight of these dogs were used as controls in estimating the counts on blood from the peripheral vessel; the external jugular vein and the common carotid artery were used in 4, and the femoral artery and vein were used in 4.

Discussion. With the exception of 3 instances (Experiments 2, 4 and 11) venous blood was found to have a slight to fairly marked increased platelet count as compared with the arterial; this applies not only to the splenic vessels, but to the peripheral vessels as well. We offer no explanation for this difference. Krumbhaar and Musser point out that venous blood often shows more or less marked anisocytosis, and an inequality of staining which are not seen in blood from the artery, and that control smears from peripheral veins

TABLE I.—PLATELET, ERTHROCYTE, AND LEUKOCYTE COUNTS OF FROM THE SPLENIC ARTERY AND VEIN OF DOGS.

Experiment.	Blood platelets.							Erythrocytes, millions.		Leukocytes.	
	Splenic artery.			Splenic vein.			Per cent venous compared with arterial. Arterial equals 100 per cent.				
	Highest count.	Lowest count.	Average, 4 to 8 counts.	Highest count.	Lowest count.	Average, 4 to 8 counts.		Splenic artery.	Splenic vein.	Splenic artery.	Splenic vein.
1	384,000	358,000	371,000	450,000	424,000	437,000	117.9	5.32	5.26	11,350	10,750
2	316,000	184,000	266,000	158,000	98,000	122,000	45.9	5.21	6.03	31,750	31,250
3	960,000	196,000	164,000	430,000	324,000	344,000	209.8	4.52	4.55	32,600	28,500
4	512,000	236,000	331,000	598,000	318,000	324,000	94.8				
5	152,000	124,000	137,000	284,000	190,000	244,000	178.1	4.85	4.78	20,900	22,200
6	74,000	19,000	49,000	148,000	51,000	104,000	212.2	4.82	4.53	14,400	17,500
7	122,000	32,000	74,000	120,000	52,000	88,000	118.1	5.11	4.97	13,900	16,400
8	262,000	62,000	124,000	330,000	121,000	187,000	150.8	5.10	4.97	12,900	13,500
9	216,000	84,000	138,000	220,000	164,000	182,000	132.0	2.97	2.93	31,400	32,100
10	174,000	146,000	158,000	236,000	216,000	225,000	143.0	5.89	5.90	18,400	18,700
11	564,000	406,000	453,000	342,000	302,000	300,000	66.0				
12	295,000	269,000	282,000	476,000	452,000	464,000	164.5				

show changes in the red cells similar to those in the red cells from the splenic vein, which indicates that these changes are characteristic of venous blood in general. However, only materially improved methods of studying blood and counting platelets can determine accurately what is the normal difference between venous and arterial counts. We have proved to our satisfaction that in the dog the platelet content of the splenic vein is not normally reduced below that of the splenic artery. This fact is in keeping with physiological principles, for there is no reason for assuming *a priori* that the platelets or any other blood corpuscle should be materially reduced in number, under normal conditions, by a single passage through the spleen.

TABLE II.—PLATELET COUNTS IN PERIPHERAL VESSELS OF DOGS.

Experiment number.	Blood platelets.		Per cent venous compared with arterial. Arterial equals 100 per cent.
	Common carotid artery (average count).	External jugular vein (average count).	
13	355,000	462,000	130.1
14	210,000	360,000	171.4
15	148,000	197,000	133.1
16	97,000	261,000	270.1
	Femoral artery	Femoral vein	
17	316,000	365,000	101.1
18	76,000	342,000	450.0
19	115,000	197,000	171.3
20	122,000	314,000	257.3

The relationship of the spleen to platelet destruction in thrombocytopenic purpura has not yet been determined. The production in animals, by the injection of a specific antiplatelet serum, of a condition which most closely resembles hemorrhagic purpura is said not to be influenced by previous splenectomy (Sacerdotti).[11] In view of the fact that it has been demonstrated that normal venous blood in general shows higher platelet counts than arterial, the finding of reduced platelet counts in blood from the splenic vein as compared with the splenic artery in thrombocytopenic purpura would have especially definite importance. There would then be good grounds for assuming that the spleen is primarily concerned in the production of this syndrome, and that splenectomy is essentially a rational procedure.

Conclusions. 1. In a series of controlled experiments performed on dogs for the purpose of determining the relative platelet content of the splenic artery and vein, we have found that the blood-platelet content of the splenic vein is not normally below that of the splenic artery.

2. The blood-platelet content of the venous circulation in general is apparently slightly elevated over that of the arterial.

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TWO NEW ANTIMONY COMPOUNDS FOR INTRAVENOUS USE*

A Study of their Therapeutic Value in Cases of Granuloma Inguinale.

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A preliminary report was published in 1923 on the use of two new synthetic antimony drugs, (sodium antimony thioglycollate and the triamid of antimony thioglycollic acid), in the treatment of granuloma inguinale. Included in this report was the result in therapy as observed in 3 cases. It is the purpose of this communication to complete the study of these drugs, present further evidence of their therapeutic value, to state their chemical composition and to incorporate toxicity studies in presenting them to the medical profession.

In the former article, 3 cases were cited of granuloma inguinale

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in each of which splendid therapeutic results were obtained. In 1 of them a disease of fifteen years' duration was cured in seventeen days with but 9 intravenous injections, without reaction, and the patient proven free of recurrence six and a half months later. As such had not been accomplished before and only approached by treatment with tartar emetic; as this latter drug is known to be toxic; as its stability is questioned when subjected to heat for sterilization; as it presents at times alarming symptoms; as it has been held responsible for an occasional death; and as it (practically always when pushed to therapeutic effect, and even occasionally, when given in moderate doses) causes reactions in the way of bone aches, dyspnea, and so on, making some patients refuse its advantages; and finally as further experience has shown the therapeutic value and low toxicity of these new drugs to have far-reaching advantages over tartar emetic—it became desirable that our subsequent experience with them be published and that they be placed within the reach of all.[1]

History. Sodium antimony thioglycollate (hereafter referred to as S. A. T. for brevity) has been known to chemists for a long time, while the triamide of antimony thioglycollic acid (hereafter referred to as T. A. T.) was first synthetized by Dr. John J. Abel, professor of pharmacology, Johns Hopkins University. Both drugs were the subject of two articles by Abel and Roundtree in experimental trypanosomiasis. Their experimental work on animals with these drugs, though carried on for trypanosome infections, gave sufficient scientific background as to their toxicity and efficacy to warrant the trial of their use in clinical cases without further animal studies, and even suggested their possible therapeutic value. This was fortunate as lesions of granuloma inguinale have not yet been successfully produced in the lower animals. One of them (T. A. T.) had never been used in man before. It was the preparation administered to the above cited case, of fifteen years' duration, in our preliminary report. Twelve or more years ago, Dr. Abel forwarded to some friends in India, some of the sodium antimony thioglycollate (S. A. T.) for use in kala azar and filariasis, but no report of its use has as yet been made, either to the profession or to Dr. Abel personally. So it might be said that the initial use of both drugs in infectious conditions in man occurred in the original cases of the preliminary report.

These original 3 patients were given the drugs as prepared and forwarded to me by Dr. Abel. Each consisted of 1 gm. in semicrystalline form, and represented the last he had at the time in his possession. The striking therapeutic results seen in these 3 patients, stimulated the desire for further studies with the drugs,

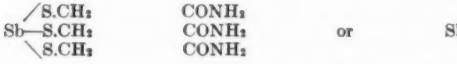
[1] Samples of these drugs have been forwarded by Hynson, Westcott & Dunning, of Baltimore, to the Council on Pharmacy and Chemistry of the American Medical Association for their study.

and their synthesis was placed in the hands of Hynson, Westcott and Dunning of Baltimore. Through their coöperation and skill their preparation was furthered and the drugs purified into perfect crystalline substances in each case, and the following experimental work has been performed with material prepared by them.

Chemistry. 1. *Sodium antimony thioglycollate* (antimony sodium thioglycollate) is a white powder, very soluble in water and having a structural formula as follows:

Its antimony content is 37.17 per cent. The aqueous solution can be sterilized by boiling without chemical change other than the separation of a very small amount of antimony sulphide, which can be removed by filtration under sterile conditions.

2. *Triamide of antimony thioglycollic acid*, or possibly better called antimony thioglycollamide, crystallizes in white glistening plates, m. p. 116.5°–118° C. (uncorr.) and has the following structural formula:



Its antimony content is 30.77 per cent. At ordinary temperatures, 100 cc of water dissolves about 0.5 gm. When this solution is cooled, some of the compound crystallizes out. It is much more soluble in boiling water, from which it can be crystallized. When pure, it is stable in air, otherwise it turns yellow. A solution can be sterilized at boiling water temperature without chemical change, other than the separation of a trace of antimony sulphide, which can be removed by filtering under sterile conditions.

The presence of a precipitate of antimony sulphide is to be avoided in administering either drug. It appears as a rusty-colored sediment and probably increases the toxicity. It can always be safely removed by filtration.

Toxicity.* Toxicity studies with these two drugs have been carried on by intravenous and subcutaneous injections in mice.

The antimony content is as follows: T. A. T. 30.77 per cent; tartar emetic 36.16 per cent and S. A. T. 37.17 per cent, and in this ratio one might expect to find their toleration.

Tartar emetic was tried first to determine its point of lethal

* I am indebted to Dr. A. E. Bothe of the Urological Service for the study of the toxicity of these drugs. He carried out the work in the Laboratory of Surgical Pathology, University Hospital, under the guidance of Dr. A. N. Richards, professor of pharmacology, and with exceptional skill, accuracy and ingenuity, administered the intravenous injections in mice.

dosage on intravenous injection. Two out of 2 mice were killed inside of three hours' time by a dosage of 0.1 mg. per gram of body weight. Decreasing this to 0.08 mg. per gram of body weight, killed 3 out of 3 mice in the same length of time. When decreased to 0.05 mg. 2 out of 5 lived, and at a dosage of 0.025 mg. there were no deaths in 4 animals; thus fixing the safe dosage at the latter figure and the sure lethal dose at 0.08 mg. per gram of body weight.

The T. A. T. preparation showed a similar point of lethal dosage. It killed 3 out of 3 mice within three hours when given both in the 0.1 mg. and 0.08 mg. dosage. At 0.05 mg. per gram of body weight only 1 out of 4 mice died (75 per cent lived as compared to 40 per cent with tartar emetic in similar dosage) while with 0.025 mg. again 4 out of 4 lived. This shows slightly less toxicity, though the safe and lethal dosage remains the same.

The S. A. T. preparation was better tolerated. At the above lethal dosage of 0.08 mg. per gram of body weight, only 1 out of 4 mice died. Increasing the dosage ot 0.1 mg., 5 out of 6 animals succumbed in from forty minutes to sixty hours, and only when 0.25 mg. was given was death caused in 2 out of 2 mice. Decreasing the dosage 0.05 mg., a slight discrepancy occurred and death in from twenty-four to forty-eight hours occurred in 2 out of 5 mice. (At this dosage, 75 per cent lived under T. A. T., 60 per cent lived under S. A. T., and only 40 per cent lived under tartar emetic.) Again at the dosage of 0.025 mg. per gram of body weight, 4 out of 4 lived. In this preparation, though the safe dose remains the same as tartar emetic and T. A. T., the higher doses appear to be less toxic. (Table I.)

TABLE I.—INTRAVENOUS INJECTIONS.

		Dose in mg. per gm. of body weight.					
		0.02	0.025	0.05	0.08	0.1	0.25
Tartar emetic	Injected	..	4	5	3	2	
	Died	..	0	3[3]	3[1]	2[5]	
T. A. T.	Injected	..	4	4	3	3	
	Died	..	0	1[1]	3[1]	3[1]	
S. A. T.	Injected	1	4	5	4	6	2
	Died	0	0	2[3]	1[4]	5[5]	2[6]

[1] Deaths inside three hours.
[2] Deaths between six to forty-eight hours.
[3] Deaths between twenty-four to forty-eight hours.
[4] Deaths inside four hours.
[5] Deaths between forty minutes to sixty hours.
[6] Deaths inside one hour.

A short series in which these two drugs were given subcutaneously showed decidedly more favorable results as compared to tartar emetic. Tartar emetic killed the 1 mouse in which it was injected in both 0.1 and 0.05 mg. dosage; it was sub-lethal when injected in 0.02 and 0.01 mg. dosage in each of 2 mice. The T. A. T. preparation was non-lethal in 5 animals (mice); 2 received 0.05 mg.,

2 received 0.08 mg. and 1 was given 0.1 mg. per gram of body weight. Likewise the S. A. T. preparation did not kill 5 mice in which it was injected subcutaneously: 2 were given 0.01 mg., 1 was given 0.05 mg., and 2 were given 0.1 mg. per gram of body weight. (Table II.)

TABLE II.—SUBCUTANEOUS INJECTIONS.

		Dose in mg. per gm. of body weight.					
		0.01	0.02	0.05	0.08	0.1	0.25
Tartar emetic	Injected	1	1	1	..	1	
	Died	0	0	1	..	1	
T. A. T.	Injected	..	..	2	2	1	
	Died	..	..	0	0	0	
S. A. T.	Injected	2	..	1	..	2	
	Died	0	..	0	..	0	

Summarizing our toxicity studies briefly, it appears that the S. A. T. preparation, though having the highest antimony content is the least toxic of the three antimony compounds, both intravenously and subcutaneously, though its safe intravenous dosage is equivalent to that of tartar emetic. The toxicity of the T. A. T. preparation stands between the two others, though again its safe intravenous dosage is equivalent to tartar emetic. In behalf of this latter drug (T. A. T.) it is to be said that its low solubility rendered it necessary to give to mice a larger bulk injection than was used in administering the other drugs, a technical difficulty, and a lethal factor not to be forgotten. Subcutaneously, both the T. A. T. and S. A. T. preparation are far less toxic than tartar emetic.

Figuring these results into terms of dosage for man, one finds that the safe dosage of 0.025 mg. per gram of body weight is the equivalent of a dosage of 1.7 gm. to a man of 150 pounds. This is exactly seventeen times more than what has been used as the maximum dosage in clinical cases, and by means of which most satisfactory therapeutic results have been obtained .

Dosage. In the preliminary report it was pointed out that on Dr. Abel's suggestion the dosage of these new drugs was to be judged by keeping it within the limitation, as to antimony content, as compared with tartar emetic, which we were then using successfully. We were using tartar emetic in 1 per cent strength and giving 10 cc as a maximum dose, *i. e.* 0.1 gm. of the drug. Antimony occurs in tartar emetic as 36.16 per cent of the whole. Finding the antimony content of T. A. T. and S. A. T. to closely approach that of tartar emetic, it was concluded to administer the new drugs in similar dosage to that already tried with tartar emetic, though feeling from Dr. Abel's statements that they would be less toxic, and less irritating.

T. A. T. The usual course pursued was to use T. A. T. in 25-cc dosage, it being prepared sterilized in ampules of this size. Its solubility being limited to less than ½ of 1 per cent, this size injection

was necessary to obtain 0.1 of the drug. Later 20-cc ampules of an accurate 0.4 per cent solution were used, giving a dosage of 0.08 gm. This has uniformly proven to be a non-toxic, non-irritant injection in all clinical cases, and at the same time possessing a potentially high therapeutic value. At no time has there been seen any symptoms of intolerance such as we had been used to expect when tartar emetic was administered in maximum dosage, and in several patients who were intolerant to tartar emetic, or regularly developed bone aches, attacks of dyspnea, and coughing spells, after tartar emetic injection, were found to take this drug without the slightest inconvenience. (Cases III, V, VII, and IX.)

Constant urinalysis failed to demonstrate any kidney irritation, the same have been omitted from case protocols for sake of brevity, and likewise no evidence of irritant action on the vein walls at the site of injection has been observed.

Our toxicity studies on this drug have proved that the dosage used clinically is one-seventeenth of the safe dosage in experimental animals judged on body weight, and it does not seem necessary from a therapeutic standpoint to administer any larger amounts. This places the $\frac{C}{T}$ dose ratio, *i. e.*,

$$\frac{\text{Curative dose, or dose sufficient to destroy all parasites}}{\text{Toxic dose, or maximum dose which the patient can tolerate}}$$

well within the accepted limit, which to be of value, Ehrlich maintained, should be not greater than one-third.

S. A. T. With S. A. T. whose antimony content is slightly greater than that of tartar emetic, we again adhered to a similar maximum dosage of 0.1 gm. Its solubility being high, it has been used in both a large dilution of 20 cc of a 0.5 per cent solution, and also in the more concentrated form of 10 cc of a 1 per cent solution. It likewise has proven devoid of irritative effect locally as administered and has been borne by all patients without reaction suggestive of antimony intoxication.

Toxicity studies on this drug have shown that it is relatively more safe than either tartar emetic or T. A. T., and clinical observations have likewise left an impression that the patient receives it more kindly.

Administration. Intravenous injection has been the rule because of the violent irritant action which we had learnt to expect when tartar emetic was injected extra-venously. This intravenous administration has given uniformly excellent therapeutic results and without evident general, local, or vascular irritation.

Intravenously, either of the drugs should be given every second day to obtain prompt and successful results.

In 7 cases daily injections were given and received without evidence of intolerance and without symptoms of reaction. (Cases

I, II, III, IV, V, VI and VII.) In 1 patient (Case VI) weekly injections were given for a period of time, only to find the lesion remain almost stationary, and his subsequent healing seemed delayed, though evidencing no recrudescence. It has been a rule to start treatment with a fraction of the considered maximum dose of 0.1 gm., in using either drug. However, several patients (Cases IV, V and VII) were given this maximum dosage as their initial injection and no reactionary symptoms were manifested.

Although prompt healing was observed in all these cases, experience has shown that one is dealing with a very chronic infection, in fact ofttimes a lesion of many years duration; also recurrences are not rare and generally appear about the periphery of the healed lesion. These facts have emphasized the necessity of continuing treatment long after apparent healing by epithelialization has occurred, if one wishes a permanent cure, and we have advised all patients to receive at least 12 injections after his first healing has taken place. It has been interesting to note in some of our old patients that the rather marked and characteristic edema that frequently accompanies a granuloma of soft tissues will ultimately disappear entirely if treatment is persisted in.

In subsequent conversations with Dr. Abel, he assured me that subcutaneous injections in his experimental rats were without apparent irritant or suppurative action. On this authority we have started studies along this line which will be the subject of a future communication, using the drugs both subcutaneously and intramuscularly. If such prove possible, and our experience so far seems to point that they will, it would be a tremendous asset in antimony therapy. (See Case histories IV, VII and IX.[1])

Case I.—R. F., a colored male, aged twenty-seven years, entered the Philadelphia General Hospital, August 5, 1922, complaining of large swelling of the scrotum. The onset was eighteen months ago as a small sore on the foreskin. This was painless, caused no discomfort but spread slowly with marked phimosis. A private physician gave him a "dorsal slit," and because of the accumulation of pus, the prepuce was likewise, at a later date, opened on the ventral surface. Following this, his entire external genitalia began to swell. He received a course of injections in the arm (most likely arsphenamin) but no improvement followed. Six months from the

[1] No local irritation was observed in the animals where injections were given subcutaneously. To date (May 1, 1924) 2 further patients have received 12 intramuscular (gluteal) injections of S. A. T. (2 cc of a 5 per cent solution). They have all been received without evidence of suppuration, and with but slight transient sensations of dull pain. Fourteen intramuscular injections of T. A. T. have been administered. The low solubility of this drug, necessitating greater bulk injections, is strongly against its intramuscular use. Two of these did suppurate, 1 given in the deltoid on the nineteenth day, the other (gluteal) on the thirty-third day; each received 12 cc of the solution and faulty technic in syringe sterilization (immersion in alcohol) might have played an important part.

onset of his trouble his scrotum was swollen to the present size; the penis disappeared into the swollen mass and a series of open lesions appeared on the skin of the scrotum. At no time has he suffered any marked discomfort or pain. Physical examination is negative except for genitalia. Scrotum presents a tumorous mass 8 inches in diameter. Entire surface is raw and covered with a granulating lesion and presents several sinuses through which urine has passed. Penis is completely lost in the tumor. In the right groin is a characteristic granulomatous area. Urinalysis and blood count were essentially normal.

Blood Wassermann. Negative.

August 9, 1922. Smear positive for granuloma organisms.

August 11, 1922. Culture positive for granuloma organisms.

The patient was placed upon intravenous injections of T. A. T. The drug was prepared in 25-cc glass ampules containing 0.4 per cent solution. His first injection consisted of a half ampule, which was increased so that by the fourth injection he was taking the full ampule dosage. This dose is equivalent to 0.1 per cent of the drug. Injection given on the following dates: August 8, 9, 10, 11, 13, 14, 15, 16, 17 and 18.

August 21, 1922. Lesions are today covered with epithelium and healed.

Swelling of the scrotum has not decreased in size, though it is very much softer. He has not at any time suffered any reaction to injections other than the local benefit observed in his lesions by rapid healing. A full-size dosage was administered on the following dates: August 29, 30, September 5, 6, 7 and 8.

September 11, 1922. Patient was this day changed from injection of the above drug to tartar emetic, 10 cc of a 1 per cent solution being given, which was repeated on September 13 and 16.

On November 15, a plastic operation was performed by the attending surgeon (Dr. Elwood Kirby). The thickened scrotal wall was for the greater part excised and the penis reconstructed with a skin covering. He received 17 further injections of tartar emetic and was discharged February 2, 1923, in a completely healed condition and remarkably improved.

He received 16 injections of T. A. T., totaling 1.41 gm. of the drug and obtained a complete healing of all open lesions.

CASE II.—J. S., a colored male, aged thirty-nine years, was admitted to the Philadelphia General Hospital June 19, 1922, complaining of sores in both groins of eight years' duration. Contracted disease while in the south, starting as a "chancroidal" sore in 1914 complicated with bilateral bubo. (Patient was admitted to this hospital in 1916 for lesions in both groins. He was treated by roentgen-ray exposures and healed in six months. About one

and a half years later groins again became the seat of open lesions which "he worried along with" until 1920 when a second admission to this hospital occurred and he was again treated by roentgen-ray and almost healed in ten weeks' time. Nine months ago the lesions again became active and spreading, and have continued to increase in size from that time to this his third admission at the above date.) The sores are now larger than they ever have been. There is pain on motion but no loss of weight. Examination is unimportant except for genitalia. In each groin is a sore 3 inches long, 1 inch wide. On the left this spreads down to the scrotal-thigh fold. It is covered with typical granulation tissue and devoid of exudate other than a moist mucus. There is no odor, nor undermining. The same process involves the under portion of the foreskin.

June 26, 1922. Blood Wassermann was negative. Spinal fluid Wassermann was negative. Smear negative for granuloma organisms.

June 20, 1922. On account of typical lesion and history, treatment started in spite of negative bacteriological findings. Patient was given 10 cc of 0.4 per cent solution T. A. T. intravenously. There was no reaction. Persistent pains in lesions were relieved immediately following the injection of the drug.

July 2, 1922. Patient given 20 cc of 0.4 per cent solution of T. A. T. intravenously. Edges of granuloma lesions drying up.

July 3, 1922. Given 20 cc 0.4 per cent solution T. A. T. intravenously. There is marked shrinkage in lesions; no pain since first injection. Owing to the limited supply of the drug, this patient received on July 4, 5, and 6, 10 cc of 1 per cent solution tartar emetic without pain or reaction.

July 7, 1922. Given 20 cc of T. A. T. intravenously. This dose was repeated on the following dates: July 9, 11, 14, 15, 16, 17 and 18. On this date the lesion on penis is flat, dry, nearly healed; groin lesions show marked epithelial proliferation and drying of lesions; complete absence of pain since first injection; in fact the lesions today are covered with epithelium, though the redundant watery proliferating nodules about the same have not disappeared but show marked shrinkage in size.

The above dosage of T. A. T. was given intravenously on the following dates: July 19, 20, 22, 24 and 25.

July 26, 1922. On account of disorderly conduct this patient was today discharged from the ward to the out-patient department. His lesions are practically healed, though he is to continue injections of tartar emetic at weekly intervals.

Final Note. September 15, 1923. This patient has been regular in attendance at the out-patient department and has remained completely healed to date. He received 16 injections of T. A. T. totaling 1.24 gm., plus 3 injections of tartar emetic, to a complete cure.

CASE III.—C. W., a colored male, aged twenty-three years, was admitted to the Philadelphia General Hospital July 22, 1922, complaining of sore on the penis. The present lesion is of seven years' duration; started as a soft painful sore on the prepucial margin which was healed under local treatment in sixty days. It remained healed however only four or five months when it broke out again and extended along the shaft of the penis toward the body. It was again treated with local applications and apparently healed for a period of five months; again returned and continued as an open sore until the present time. (In 1917–1918 he received 10 injections of cacodylate of soda, and later he was given 8 injections of mercury and a series of intravenous injections of neosalvarsan in the arm. He has had no medical treatment during the past year.) Physical examination unimportant except for genital lesion. Beneath the glans penis is a large irregular area (an effort was made in 1919 to excise the growth but was unsuccessful and recurrence promptly appeared) of an old operative wound. Around this is redundant, hard, smooth, skin and approximal to this is an elevated nudular tender growth; its surface is covered with soft granulation tissue. There is marked induration of all the loose cellular tissue over the shaft of the penis about the lesion. The glans is not involved; the lesion seems to be quite painful to handling.

July 23, 1922. Urinalysis: essentially normal. Leukocytes, 8700; hemoglobin 54 per cent; red blood cells 5,340,000.

July 24, 1922. Blood Wassermann positive; smear and culture positive for granuloma organisms.

August 7, 1922. On account of the presence of a positive Wassermann, the patient was given 2 injections of neosalvarsan, also inunctions of mercury, and potassium iodid in increasing doses to date without any apparent improvement in his local condition. Today he was given 10 cc of 0.4 solution of T. A. T. intravenously.

August 8, 1922. Given 17 cc of 0.4 per cent solution T. A. T. intravenously.

August 9, 1922. Given 18 cc of 0.4 per cent solution T. A. T. intravenously.

August 10, 1922. Given 19 cc of 0.4 per cent solution T. A. T. intravenously.

On the following dates he was given 20 cc of 0.4 per cent solution T. A. T. intravenously: August 11, 13, 14, 15, 16, 17 and 18. (The pain in the lesion, which was rather severe, completely disappeared following the first injection and has been absent ever since.) On the last date the lesion is reported as being dry and rapidly healing and marked shrinkage in the heavy indurated tissue. The above dosage was repeated on August 19, 30 and 31.

September 1, 1922. There are still some moist areas in the lesion, though the anterior and posterior portion are greatly improved.

On the following dates 20 cc of 0.4 per cent solution T. A. T. was

given intravenously: September 1, 2, 5, 6, 7 and 8. It is to be noted that the patient has not suffered any reaction at any time from this drug; as his healing has been slow to date, it was thought wise to try him on tartar emetic.

September 11, 1922. Given 10 cc of 1 per cent solution tartar emetic intravenously.

September 12, 1922. Patient has a rather sharp reaction to the above injection with persistent pains in the long bones; some dysuria and cardiac palpitation.

September 13, 1922. Given second injection of 10 cc of 1 per cent solution tartar emetic intravenously.

September 14, 1922. Patient again suffered a reaction to the injection, more severe than on the prior dosage.

September 16, 1922. Patient given 10 cc of 1 per cent solution of tartar emetic intravenously; immediately suffered a violent reaction, coughing, vomiting, dizziness and rapid breathing.

Fearing further toxic reactions from tartar emetic, 20 cc of 0.4 per cent solution T. A. T. was given intravenously on September 23 and 27. There was no reaction.

October 2, 1922. Patient requested his discharge. Lesion on the penis has shown slow but progressive improvement. There are at present no raw areas and the lesion is completely covered with epithelium. There has been a decrease of about one-third in the heavy induration underlying the growth. Patient was discharged to the out-patient department for continuation of treatment.

COMMENT. He received at first 18 injections of T. A. T., totaling 1.556 gm. of the drug without the slightest reaction. He then received 3 injections of tartar emetic each of which was followed by increasingly alarming symptoms that demanded their cessation. He was then given 2 further injections of 20 cc each of 0.4 per cent solution T. A. T., totaling 0.16 gm. without any reaction whatsoever.

CASE IV.—W. G., male, colored, aged twenty-two years, was admitted to the Philadelphia General Hospital June 17, 1922, complaining of a sore in the right groin and a lesion on the penis. These are of two and a half years' duration and developed after circumcision for chancroid and the opening of a right inguinal bubo. Examination of the genitalia presented an old sore on the frenum which has remained since circumcision for chancroid (?) in 1919. In the right groin is a typical granuloma lesion 2 inches long by $\frac{3}{4}$ of an inch wide with redundant edges and no undermining.

June 19, 1922. Blood Wassermann is negative.

June 20 and 26, 1922. Smears negative for granuloma organisms.

June 21 and 27, 1922. Cultures negative for granuloma organisms.

June 30, 1922. Patient given 5 cc of 0.4 per cent solution T. A. T. subcutaneously over each shoulder blade. He suffered severe pain

from the time of the injection, and required a hypodermic of ¼ gr. morphia to control it.

July 2, 1922. Given 20 cc of 0.4 per cent solution of T. A. T. intravenously.

There was no reaction and pains in his lesions which had been severe from the time of his admission were immediately relieved.

July 3, 1922. Similar dosage given intravenously followed by marked shrinkage of the edges of his granuloma. Patient has had no more pains in his lesions. On account of the scarcity of the drug, this patient had to be changed to tartar emetic, which he received at two- to three-day intervals and was healed July 24.

September 15, 1922. This patient has been in regular attendance at the out-patient department and has remained healed to date.

COMMENT. He received 10 cc of 0.4 per cent solution T. A. T. subcutaneously; this caused pain. He was subsequently given two doses of 20 cc each of 0.4 per cent solution T. A. T. intravenously with marked relief of pain in his lesions and improvement in their condition, followed by tartar emetic to a permanent cure.

CASE V.—W. F.,[1] male, colored, aged thirty-five years, was readmitted August 23, 1922, with a recurrence of the anal lesion that appeared four weeks after leaving the hospital; the recurrence occurring principally about the periphery of the old lesion and extending forward to the perineum and to the scrotal attachment. He was placed again on tartar emetic treatment, being given 10 cc of a 1 per cent solution on alternate days. He seemed now particularly susceptible to tartar emetic and after each injection he was laid up the following day with bone pains and always had a severe coughing spell of ten to twenty minutes' duration immediately following the injection.

September 18, 1922. Patient was given a full dose of T. A. T. (0.1 gm.) without any reaction whatsoever. This dosage was repeated on the following dates: September 27, 29, 30, 31, October 5, 6, 11, 13 and 16. There was no recurrence of his intolerance to antimony as seen when tartar emetic was used and each dose was taken without symptoms of any kind.

October 24, 1922. The patient reports anal lesion is completely healed. Patient discharged to a hospital physician for observation.

February 15, 1923. Patient left the hospital physician today. He has remained healed from the time of his last injection to the present date, now four months past. He received 10 injections of T. A. T., totaling 1.0 gm. of the drug and received the same without the reactions that had caused tartar emetic to be almost prohibitive.

[1] This patient was Case VI of our published series in Surgery, Gynecology and Obstetrics (June 1, 1922). He was on that admission discharged, April 23, 1922, for further treatment in the out-patient department, which he failed to follow.

CASE VI.—C. D., A. 3972, male, colored, aged twenty-six years, entered the out-patient department University of Pennsylvania Hospital, May 8, 1923, with an ulcer in the coronal sulcus on the right, of nine days' duration. Dark field was negative; repeated again the following day and again found to be negative. Wassermann was likewise negative. The lesion was treated as a chancroid and patient disappeared from observation on May 25 practically healed. Wassermann taken under date of last visit was strongly positive.

Returned to out-patient department September 1, 1923, with a triangular area measuring 4 x 3 x 3 cm. in the midline in the pubic hair region that was covered with a scab, and practically painless, and overlying a deep-seated induration which extended downward to the right lateral side of shaft of penis, and to the region of the external inguinal ring. He gave a history of having had an abscess at this situation, which was opened, and had likewise been given some injections of salvarsan before returning to us.

September 5, 1923. Smear positive for granuloma organisms.

September 8, 1923. Given 15 cc of 0.5 per cent solution S. A. T. intravenously.

September 12, 1923. Given 20 cc of 0.5 per cent solution S. A. T. intravenously.

September 15, 1923. Given 20 cc of 0.5 per cent solution S. A. T. intravenously. Lesion shows healing about periphery.

September 19, 1923. Given 20 cc of 0.5 per cent solution S. A. T. intravenously.

September 24, 1923. Given 20 cc of 0.5 per cent solution S. A. T. intravenously.

Deep seated induration has practically disappeared and lesion is dry, painless, and covered with a scab which is easily removed, showing a surface three-fourths covered with epithelium; remainder with soft bleeding granulation tissue.

The patient was given the above dosage on the following dates: September 29, October 5, 13, 27, November 3, 26 and December 1. These last injections were given at weekly or greater intervals, and there was a cessation of the rapid healing and though progress was obtained, it was not as consistent as when injections were given at shorter intervals. Feeling that it might possibly be due to his syphilitic infection, the patient was given during the months of December and January weekly injections of neosalvarsan, and on the following dates the patient was given 20 cc of 0.5 per cent solution S. A. T. intravenously: January 25, 26, 31, February 1, 2, 6, 9 and 14. The patient was lost to observation following this last injection; the lesion is recorded as healed on the visit of February 2, 1924.

CASE VII.—A. H., A. 4974, aged thirty-eight years, a colored male, was admitted to out-patient department February 12, 1924,

complaining of sore on penis of ten days' duration. Started like a small boil. A few days after onset, patient picked top off and scab formed. The scab has been rubbed off several times. The lesion was at the base of penis, on dorsal surface, is perfectly circular and 2 cm. in diameter, with a small papule at one edge. The lesion was covered with a crust-like formation. This crust was removed and smear made, which was positive for granuloma organisms. Second papule is just breaking at pubic hair margin in right groin.

February 13, 1924. Given 20 cc of 0.5 per cent solution S. A. T. intravenously.

February 15, 1924. No reaction. Given 20 cc of 0.5 per cent solution S. A. T. intravenously.

February 18, 1924. Given 3 cc of 1 per cent solution tartar emetic intravenously. Healing has started with epithelial proliferation about edge.

March 20, 1924. Because of the scarcity of the new drug, patient has been given tartar emetic in 0.05 to 0.1 gm. dosage on the following dates: February 21, 25, 28 and March 3, 6, 13, 14 and 18 and today. These treatments were all given in the dispensary and patient recounts that though no disagreeable symptoms have followed, rheumatoid pains in the shoulders have been constantly present for twenty-four hours after injection. Lesion today is healed except for a slight portion about periphery that persists in scabbing over. Lesion in pubic hair region has disappeared completely.

March 21, 1924. Given 10 cc of 0.5 per cent solution S. A. T. in right gluteus and 10 cc intravenously. Developed slight coughing spell of fifteen minutes' duration, without other symptoms. This is the first symptom of this kind observed with this drug and possibly due to giving drug the day following tartar emetic.

March 24, 1924. Given 10 cc of 0.5 per cent solution S. A. T. in left gluteus and 10 cc intravenously. There was no reaction. The previous intramuscular injection caused no discomfort.

March 27, 1924. Given 20 cc of 0.5 per cent solution S. A. T. intravenously. Gluteal muscles sore to deep pressure; no pain; no lump. Vomited after leaving dispensary.

April 1, 1924. Given 20 cc of 0.5 per cent solution S. A. T. intravenously. Gluteal muscle less sore. He had a sharp "nitritoid" reaction. (*N. B.*—These last 3 S. A. T. injections are from a new lot. Another dose given to a new patient likewise caused reaction: Solution slightly colored and undoubtedly not pure.) Lesion completely healed.

April 8, 1924. Given 10 cc of 0.4 per cent solution T. A. T., no reaction.

April 11, 1924. Given 20 cc of 0.4 per cent solution T. A. T., no reaction.

April 15, 1924. Given 20 cc of 0.4 per cent solution T. A. T. no reaction.

April 22, 1924. Given 20 cc of 0.4 per cent solution T. A. T., no reaction. Gluteal muscles normal.

NOTE.—October 8, 1924. Patient has taken 28 full doses of T. A. T. since the above date, all devoid of any reaction.

CASE VIII.—McK. T., A. 3358, a colored male, aged twenty-one years, entered the dispensary November 28, 1922. Developed a small sore on glans penis with swelling of prepuce two years ago, which has remained since as a painless lesion. Recently a second open sore appeared on under side of prepuse, which is raw, red and covered with granulation tissue. There is no undermining; no discharge; practically no pain. There is heavy chronic edema of the distal half of penile skin, and the prepuce is rendered irretractible by the same.

November 29, 1922. Smear negative for granuloma organisms. Urine shows trace of albumin; occasional red blood cell and white blood cell.

December 2, 1922. Smear again negative for granuloma organisms.

December 9, 1922. Smear is positive for granuloma organisms. Given 7 cc of 1 per cent solution S. A. T. intravenously.

December 11, 1922. Given 8 cc of 1 per cent solution S. A. T. intravenously.

December 13, 1922. Given 9 cc of 1 per cent solution S. A. T. intravenously. Sore is rapidly covering with epithelium.

December 15, 1922. Given 10 cc of 1 per cent solution S. A. T. intravenously.

December 17, 1922. Given 15 cc of 0.4 per cent solution T. A. T. intravenously.

December 19, 1922. Given 15 cc of 0.4 per cent solution T. A. T. intravenously.

December 22, 1922. Given 20 cc of 0.4 per cent solution T. A. T. intravenously. Lesions are now healed; prepuce retractible.

Patient was advised to continue treatment but was lost to further observation. He received 4 injections of S. A. T., totalling 0.24 gm. of drug, and 3 injections of T. A. T., totaling 0.2 gm. of drug.

CASE IX.—W. R. was No. 3 of the series of cases reported in the *Journal of Urology* for June 9, 1923. At that time he gained a complete healing under sodium antimony thioglycollate and tartar emetic, being discharged on January 31, 1922 to continue his injections in the out-patient department, which he neglected to do owing to the fact that shortly after his discharge he was arrested and placed in jail. On his discharge from jail, on April 1, 1922, he already noticed a recurrence of his granuloma and was readmitted to the hospital on April 8, 1922, desperately ill with lobar pneumonia. His recovery was prompt, and on April 25, 1922 he was transferred

to the genito-urinary service for treatment of the recurrence of his granuloma. The growth appeared as a conglomerate roseola about the periphery of his primary lesion, the center of which is still covered with healthy epithelium. Smears taken at the time of his transfer on April 25 were positive for granuloma organisms.

During this patient's previous admission he had shown marked reaction after each injection of tartar emetic, but had taken S. A. T. without the slightest trouble.

May 8, 1922. Given 2½ cc of 0.4 per cent solution of T. A. T. intravenously; 5 cc of the same solution was injected subdermally. There was no reaction to either the intravenous or subdermal injection of the drug.

May 10, 1922. Given 5 cc of 0.4 per cent solution T. A. T. intravenously.

May 12, 1922. Given 10 cc of 0.4 per cent solution of T. A. T. intravenously. Lesion is beginning to heal nicely.

May 14, 1922. Given 20 cc of 0.4 per cent solution T. A. T. intravenously. Marked progress in healing. This dosage was repeated on May 16, 18, 22, 24, 28, June 1, 3, 5, 7 and 9.

June 10, 1922. All lesions are now completely healed. This dosage was continued on alternate days until June 29, 1922 when he was discharged to the out-patient department with advice to continue his injections once per week.

He received 23 injections of T. A. T., totaling 1.61 gm. with complete healing of his lesions. Tolerance to the drug was perfect and at no time were reactions obtained that had made previous tartar emetic medication perilous.[1]

Case X.—W. MacL., A 3624, male, colored, aged twenty-six years, entered the dispensary of the University of Pennsylvania Hospital, February 7, 1923. He was circumcised two years ago, at which time he had an ulcer on right side of prepuce; circumcision scar refused to heal and ulceration has persisted to present time. Lesion appears as a narrow granulomatous sore along the line of scar of circumcision under which is a heavy indurated edematous condition of the surrounding skin. Smear is positive for granuloma organisms. Wassermann, negative.

February 7, 1923. Intravenous administration of 6 cc of 0.4 per cent solution of T. A. T.

February 17, 1923. Intravenous administration of 10 cc of 1 per cent solution S. A. T.

February 20, 1923. Intravenous administration of 10 cc of 1 per cent solution of S. A. T. Lesions are completely healed over. This dose of 10 cc of 1 per cent solution of S. A. T. was repeated on the following dates: February 20, 26, March 1, 5, 13, 20 and April 9.

[1] Colored drawing of this lesion is to be found in Cabot's Urology, 2d edition.

The lesion has healed completely; edema markedly improved. Patient lost to observation. This patient received 9 injections intravenously of S. A. T., totaling 0.9 gm. of the drug without reaction; as likewise 1 injection of T. A. T.

CASE XI.—T. L., A 4437, male, white, aged sixty-three years, was admitted to the University of Pennsylvania Hospital September 25, 1923. Condition of inoperable carcinoma of the bladder involving two-thirds of the vesical wall, causing urgency and frequency of urination with marked hematuria. The drug was administered to observe effect. Patient kept in hospital to receive deep roentgenotherapy.

He received, at every two- to three-day intervals, a total of 13 injections of T. A. T., totalling 0.996 gm. of the drug. There was no visible improvement in the patient's condition; there was no reaction to the drug; no intolerance or accumulative effect seen, and no local reaction at site of venous puncture. This was purely a negative study and is reported as a case showing toleration to the drug.

CASE XII.—P. W., A. 3919, male, white, aged fifty-two years, entered the University of Pennsylvania Hospital April 23, 1923. Patient's history recorded British Army service in India and Egypt, during which he had an attack of cystitis associated with hematuria, with which a number of the men in his command likewise suffered. A most unusual cystoscopical picture was thought to be bilharziasis. The most painstaking and repeated urine examinations failed to demonstrate ova, and were likewise negative for the tubercle bacillus. Catheterized kidney specimens showed clear urine, and a differential functional test gave bilaterally equal and normal function.

The following injections were given empirically:

May 7, 1923. Given 7 cc of 1 per cent solution of S. A. T. intravenously.

May 10, 1923. Given 8 cc of 1 per cent solution of S. A. T. intravenously. Each of these injections seemed to cause a flare-up of his cystitic condition with excessive outpouring of a mucopurulent urine. Injections were delayed while further diagnostic laboratory researches were made. These proved again negative, as likewise biopsy of vesical lesion.

May 22, 1923. Given 7 cc of 1 per cent solution S. A. T. intravenously.

May 24, 1923. Given 8 cc of 1 per cent solution S. A. T. intravenously.

May 27, 1923. Given 8 cc of 1 per cent solution S. A. T. intravenously.

June 2, 1923. Given 20 cc of 0.5 per cent solution S. A. T. intravenously. This dosage was repeated on the following dates: June 7, 11, 16, 21, 28 and July 9. On the continuation of treatment no

further reactions were observed and at the end the clinical picture appeared practically unchanged. This is reported as a case showing toleration of the drug. He received 12 injections of S. A. T., totaling 1.08 gm. of the drug.

Extraneous Cases. Besides the above cited patients (Cases XI and XII) in which one of the drugs was administered for conditions other than granuloma, the S. A. T. preparation has been given intravenously to 13 other patients suffering from various infections, in order to observe its therapeutic value and tolerance. Without reporting these cases in full, it is worthy to note that 3 patients received 1 dose; 1 patient received 2 doses; 2 patients received 3 doses; 2 patients received 4 doses; 3 patients received 5 doses and 1 patient received 6 doses and another 12 doses. This is a total of 52 doses, all given intravenously. Three patients were given the full dosage of 20 cc of a 0.5 per cent solution of S. A. T. as their initial injection. They were all received without evidence of toxicity or intolerance. Four were ward patients and their urine was watched for indications of renal irritation without observing such to occur.

Discussion. Of 10 patients suffering with granuloma inguinale herein reported, 5 received the T. A. T. preparation, 4 of whom were completely healed. (Cases I, II, III and V). The fifth patient (Case IV) had to forego further treatment after 3 injections because of the scarcity of the drug to hand at the time: his healing was completed with tartar emetic. Three of the 4 cured patients (Cases I, II and III), during part of their treatment, received daily maximum dosages of 0.1 gm. over a period of four, five and six days without symptoms of toxicity or intolerance. One of them (Case III) who had received T. A. T. in such concentration without the slightest difficulty, when subsequently given tartar emetic, suffered alarming reactionary symptoms, and then again took T. A. T. without the slightest trouble. This intolerance for tartar emetic and complete toleration for T. A. T. was again observed in Cases V and IX. The complete relief of pain in the lesion immediately following the first administration of the drug was observed in 3 patients (Cases II, III and IV). One patient, and he one of the cases that was intolerant to tartar emetic (Case V), was started on the maximum dosage of 0.1 gm. with the first injection and experienced no ill-effects whatsoever. Healing in all these cases was certainly as rapid as we were accustomed to see under tartar emetic therapy, while the sense of security rapidly formed after brief experience with the drug, due to the absence of reactions observed in certain patients after tartar emetic had been administered, made one feel doubly grateful for its efficacy at all.

Two patients with granuloma inguinale were treated with the S. A. T. preparation: both were healed. (Cases VI and VII.) The first received prompt therapeutic results with a remarkable disap-

pearance of the deep-seated induration often accompanying these lesions, until the intervals between injections were allowed to lapse to weekly periods, when a definite slowing up of the healing process was observed. Subsequently, a more active therapy established the cure. During his treatment, full daily doses of 0.1 gm. were given for three consecutive days without symptoms of intolerance or toxicity. The second patient likewise handled the drug without the slightest trouble, except on one occasion when it was given the day following an administration of tartar emetic, a short coughing spell of fifteen minutes' duration ensued, without change in pulse-rate or volume or other untoward symptoms, and on the third and fourth administration of an experimental combination of this drug he showed antimony intoxication. He was then placed on T. A. T. and has taken 28 full doses to date without the slightest trouble. Tartar emetic was given to him for a short while and he regularly experienced rheumatoid pains following each injection, symptoms that were absent when taking S. A. T. He also received the maximum of 0.1 gm. on his initial dose.

The therapeutic value of this S. A. T. preparation seems equal to that of the T. A. T. drug. It is difficult to draw comparisons in so few patients, especially so when the evidence is devoid of disagreeable circumstances and is to be based only on the rapidity of healing, and that in patients whose lesions vary markedly in extent.

Three patients were given injections of both drugs for comparative results. All were cured. (Cases VIII, IX and X.) The first of these was given 4 injections of S. A. T. at second-day intervals, followed by 3 injections of T. A. T. Prompt healing ensued, and no untoward symptoms were experienced. The second had been given S. A. T. at a previous admission. He likewise developed a marked idiosyncrasy to tartar emetic and begged not to be given it. He was given 23 injections of T. A. T. on alternate days to a complete healing. His toleration of the drug was perfect. The third patient was first given 1 injection of T. A. T., and then 9 injections of S. A. T. Healing was established without the slightest reaction to either drug. This comparison allows of no conclusions.

Two further patients are reported who did not have granuloma inguinale; 1 received 13 intravenous injections of T. A. T., while the other was given 12 injections of S. A. T., and in neither was there any evidence of antimony intolerance.

Summary. There have been treated 10 cases of granuloma inguinale: 9 have been cured by these drugs alone, while the tenth was cured with tartar emetic during a period of scarcity of the new compounds. The T. A. T. preparation has been administered intravenously 102 times: it has never given the slightest evidence of toxicity, and has been productive of a cure in 5 patients suffering with granuloma inguinale. A maximum dosage of 0.1 gm. has been adhered to. The S. A. T. preparation has been injected intraven-

ously 92 times, to a similar maximum dosage, and excepting the reactions recorded and explained in Case VII, it likewise has been borne without symptoms of antimony intoxication. It has cured the 2 patients in which it was used. Two further cases were cured by the administration of both drugs. Five patients showing symptoms of intolerance to tartar emetic, have taken one or the other of the drugs with the complete absence of such symptoms. Five patients have been given the considered maximum dosage as their initial dose, and have borne the same without any symptoms. To anyone who has used tartar emetic intravenously at all extensively, such successful results, as obtained by these drugs, will come as a hopeful advance in therapy.

Conclusions. 1. There are presented two new synthetic antimony compounds for intravenous administration.

2. Studies on animals show them to be of slightly lower toxicity than tartar emetic, while clinically they have failed to show any evidence of antimony poisoning so often observed in using tartar emetic.

3. Clinically they have evidenced no toxicity in the dosages advised, while 5 patients intolerant to tartar emetic have taken these drugs without reactions.

4. Neither of the two new drugs have shown any irritative effect at the site of intravenous injections.

5. Ten cases of granuloma inguinale are reported. Prompt, and complete healing, with evident cure, has been accomplished in 9 of them by the use of these new drugs.

6. Immediate relief of pain following the initial injection has been a remarkable manifestation in 3 of the patients.

7. The value of these drugs in other infectious conditions, where tartar emetic has proven efficacious may be expected.

8. Both preparations have been given successfully intramuscularly, though one is to be preferred.

9. As antimony belongs in that chemical group that embraces arsenic, mercury and bismuth, the possible value of these new drugs in syphilis might be expected, and is at present being studied.

Final Note. Antimony is rapidly receiving well-deserved attention as a drug of high therapeutic value when given intravenously for numerous diseases, especially those of protozoan origin and those offtimes grouped as tropical diseases. At the Ranaghat Hospital (India) 8000 intravenous injections of the salts of antimony were given in the year 1921.[1]

Reference to Abel and Roundtree's articles gives one a beautiful summary of the subject as applied to trypanosome and allied infections. Faber and Schussler in concluding their article on Leishmaniasis say: "Antimony is probably a true specific. It is still

[1] Mission Hospital, August, 1922, p. 211.

most commonly used as tartar emetic, but without doubt research will discover new combinations that are more effective and less toxic." With this in mind a bibliography is appended of recent literature concerning antimony therapy in an attempt to point out the possible conditions in which these two new synthetic drugs may gain a field of usefulness.

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EXPERIMENTAL BILIARY DRAINAGE IN THE DOG.

A Preliminary Note.

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Conflicting results have been obtained by experiments carried out on dogs to substantiate Meltzer's theory of contrary innervation between the gall-bladder and the sphincter of Oddi,[1] and Lyon's clinical application thereof.[2] These studies have chiefly concerned the question of the contractility of the gall-bladder, alone or in relation to the action of the sphincter of Oddi. They were usually conducted on dogs under the influence of depressant drugs or general anesthetics, with the abdomen open and the duodenum incised so as to expose the papilla of Vater.

In the course of a series of experiments performed under similar conditions (results to be published) we could not demonstrate contraction of the gall-bladder nor evidence of the law of contrary innervation. Interesting observations were made, however, on

[1] Meltzer, S. J.: Am. Jour. Med. Sci., 1917, **153**, 469.
[2] Lyon, B. B. V.: Jour. Am. Med. Assn., 1919, **73**, 980.

the pressure factors concerned in the biliary flow. Appreciating the many unphysiological conditions present in this type of experimentation an effort was made, as described below, to imitate as closely as possible the circumstances existing when the Meltzer-Lyon test is carried out in the human.

Under ether anesthesia a median laparotomy was performed. Through a small opening in the anterior wall of the stomach, near the greater curvature, well away from the antrum, a narrow soft tube was passed and guided through the pylorus into the duodenum and upper jejunum. Small fenestra were made in the tube at the site of the papilla of Vater. The position of the tube was made secure by a double flange on it which was brought out through a small stab wound to the left of the primary wound. The stomach wall about the tube was likewise fastened to the parietes. With a small syringe and hypodermic needle, 2 cc of bile were withdrawn from the gall-bladder and replaced by an equal amount of dye (0.5 per cent methylene blue).

If at this point the duodenum was lavaged through the tube with warm 25 per cent magnesium sulphate solution, only light brown, bile stained fluid could be recovered, without a trace of dye. When the abdominal wound was closed by suture and this test repeated, the same result was obtained.

Further observations were made on the following day, the dogs having recovered from the effects of the anesthesia. In one animal, still fasting nineteen hours after operation, lavage of the duodenum with the magnesium sulphate solution yielded only yellow-brown bile. Five hours later, twenty-four hours after operation, the dog was fed some bread and water. Half an hour after feeding, the duodenal tube was aspirated and dark blue-dyed bile was recovered (gall-bladder bile). The following day, forty-six hours after operation, lavage with magnesium sulphate yielded fluid well stained by the dye. No dye was subsequently recovered from the duodenum of this dog. At autopsy one week after operation, the gall-bladder and ducts were found free of adhesions and no dye was present in the gall-bladder bile. It seems probable that the gall-bladder had been emptied of the original dyed bile within a period of forty-eight to seventy-two hours.

A second animal, examined twenty hours after operation, yielded 3 cc of dark brown bile upon aspiration of the duodenal tube. Instillation of magnesium sulphate solution yielded 15 cc of deeply blue-dyed fluid after five minutes, followed by yellow-brown fluid free of dye. No dye was subsequently recovered from this animal. At autopsy, five days after operation, the gall-bladder and ducts were normal. About 10 cc of brown bile, without dye, was found in the gall-bladder. Here again it seems probable that the organ had been emptied within a period of forty-eight hours.

A third animal, examined sixteen hours after operation, and still fasting, yielded 5 cc of brown bile upon aspiration. Lavage with warm water yielded only light yellow stained fluid. Lavage with magnesium sulphate solution yielded deeply dyed fluid for ten minutes, followed by light yellow-brown fluid containing no dye. In subsequent tests upon this dog we failed to recover any dye. Autopsy a week after operation showed no dye in the gall-bladder bile. The gall-bladder and ducts were normal. It seemed that the organ had been emptied within twenty-four hours.

Conclusions. From the above experimental observations, it may be concluded that following the introduction of warm 25 per cent magnesium sulphate into the duodenum of the dog, bile from the gall-bladder entered the duodenum. From other studies which have been made by the authors there is evidence that magnesium sulphate does this by inducing an adequate degree of relaxation of the sphincter of Oddi. Proof of Meltzer's theory of contrary innervation was not obtained. In fact, it is our belief that the assumption of this theory is not necessary to explain the mechanism of the biliary flow. Our conception of this mechanism together with studies on substances other than magnesium sulphate will form the basis of further communications.

REVIEWS.

BASAL METABOLISM IN HEALTH AND DISEASE. By EUGENE F. DU BOIS, M.D., Medical Director, Russell Sage Institute of Pathology; Associate Professor of Medicine, Cornell University Medical College. Pp. 372; 79 illustrations. Philadelphia: Lea & Febiger, 1924.

THERE is probably no one in this country better qualified to write on the subject of basal metabolism than Du Bois who, for years, has been studying the subject experimentally and clinically. Indeed his experimental studies are as important fundamentally as any that have been produced by any authority. In addition to Du Bois's qualifications on the experimental side of the subject, he has for some years been interested in clinical experimental studies which have been of tremendous value in elucidating the problems that have arisen as a result of his experimental work. For these reasons he is well qualified to prepare a monograph on basal metabolism.

The book is divided into two main sections, the first dealing with metabolism in health, the second with metabolism in disease. Metabolism in health deals with metabolism of the carbohydrate, fat and protein molecules, the general principles of respiration apparatus, methods of calculation, normal basal metabolism, estimation of the surface area of the body and so on: a most complete exposition of the subject. Metabolism in disease, the second portion of the book deals with metabolism in practically all types of disease, and shows explicitly, discussing in detail the several diseases, that the estimation of the basal metabolism as a clinical test is of value only in certain types of disease. Lastly, he discusses in a very brief chapter the effect of drugs on basal metabolism.

From the qualifications that Doctor Du Bois has one would expect a valuable presentation. In going over the book carefully the reviewer is in no way disappointed and his expectations were fully realized. M.

THE AVALANCHE. By ERNEST POOLE. Pp. 344. New York: The Macmillan Company, 1924.

THIS work of Poole is a psychological work in which the hero, a young doctor, performs near-miracles with patients who are on the

brink of insanity. He restores them to mental health by what seems a blend of mesmerism, hypnotism, animal magnetism, faith healing, the methods of Coué, the theories of Freud, and the maxims of William James, combined occasionally with a little morphin. It is rather a pity that his mode of procedure is not given more in detail as it was so singularly successful.

His life, however, is brief, for he unfortunately marries a very able and worldly young woman who attempts to launch him on a career of practical and spectacular success by a system of camouflaged advertising. He succumbs to a weak heart and the strain on his feelings of such mismating and dies in the sympathetic company of a Hindu philosopher.

Mr. Poole is an accomplished writer, and his analysis and presentation of character are finely done, but the prominent aspect of the novel is that the hero, who is supposed to be a wonderfully admirable and gifted person (as he would of course have to be to effect his miraculous cures), appears to be fundamentally of such a visionary, credulous and vague mind as to discredit the presumption that he would have been able under the happiest circumstances to contribute much to the progress of science. It is probable that the men who are to make the great discoveries in his chosen field which the future is undoubtedly to bring must have clearer heads and be of tougher mental fiber. U.

MEDICAL QUOTATIONS FROM ENGLISH PROSE. By JOHN H. LINDSEY, M.D. Pp. 298; 8 illustrations. Boston: Richard G. Badger, 1924.

THE medical quotations that Lindsey has selected for his book come from the works of nine well known writers, some of whom were physicians and some were not, but all of whom have been interested in the subject of medicine. He has coned the works of these English writers carefully and has collected practically everything they have to say about the subject of health. The most extensive collection are from the diary of Samuel Pepys. In fact they include almost a half of the book, and as usual with this entertaining writer the quotations are trite and interesting. It will well repay the student of literary medicine to go over the book and to read the various interesting quotations. M.

BASAL METABOLISM. By JOHN T. KING, JR., M.D. Pp. 118; 14 illustrations. Baltimore: Williams & Wilkins Co., 1924.

THE ever-increasing interest in basal metabolism as a result of the application to diseased states of the experimental studies of Du Bois,

upon the metabolism of the normal individual, has made necessary a text-book such as the present one that Doctor King now presents to the medical profession. The book is well balanced, the subject matter is clearly presented and is critically selected. The limits of basal metabolic studies are well brought out as are the important clinical data derived from the method. A large series of tables and a most excellent bibliography add considerably to the value of the work. M.

Disease in Captive Wild Mammals and Birds. By Herbert Fox, M.D., Pathologist to the Zoölogical Society of Philadelphia, Director of the William Pepper Clinical Laboratory, University of Pennsylvania; with a foreword by Charles B. Penrose, M.D., President of the Zoölogical Society of Philadelphia. Pp. 665; with 28 analytical tables and 87 illustrations. Philadelphia, London and Chicago: J. B. Lippincott Company, 1924.

This volume, excellent in its production and a credit to the publishers, places upon the medical profession a real debt to its author and to the individual, past, and present members of the staff of the Pathological Laboratory of the Philadelphia Zoölogical Gardens whose work has made it possible. It is primarily a work in comparative pathological anatomy dealing with a zoölogical field which hitherto has been presented only in scattered journal articles and occasional sections of the annual reports of our larger zoölogical collections; and for this reason is virtually unique. It is based on the records of nearly six thousand autopsies performed during the past twenty years upon captive wild animals and birds which died in the Philadelphia Zoölogical Gardens. Pathology, as we know it, has been developed in connection with medical studies upon human beings, influenced of course by the contributions of modern veterinarians and those of experimental workers dealing with the small group of laboratory animals; and it is a welcome addition to have available for comparison such an analytical presentation of studies upon so large a zoölogical range, even if in the nature of all zoölogical collections, it is true that comparatively few individual specimens are included in the smaller subdivisions, *i. e.*, species and genera. That feature concerns little more than statistical questions of disease incidence, and in that scarcely more than prevalence in restricted groups, not matters of zoölogical range of any given affection.

In the nature of things to analyze adequately such a book is beyond the space reasonable for a journal review; it would almost amount to a volume itself. The writer prefers therefore to limit himself to an expression of appreciation and to a superficial and general description. The body of the work is preceded by a sym-

pathetic and very interesting and readable foreword from the pen of Dr. C. B. Penrose, President of the Zoölogical Society of Philadelphia, to whom in a large measure the establishment of the laboratory of the Gardens was due and who has for the whole period of its existence been more than merely interested in its studies, himself a trained medical man and an experienced zoölogist. In the later pages of the book are included, and have essential value, chapters by Dr. E. P. Corson-White upon the relations of diet to disease, and by Dr. F. D. Weidman in a general review of animal parasites as they have been encountered in the course of these autopsies. The bulk of the book is taken up by Dr. Fox's analytical presentation of the autopsy records, statistical, descriptive and comparative. Each system of organs or individual organs is presented, as in most treatises upon special pathology, with the particular diseases affecting it as found in the different groups in the order of accepted zoölogical classification. This arrangement in itself lends itself well to comparison, and is often elaborated by special tabulations especially upon disease incidence. As a rule each organ receives from the author some outline of its normal and comparative anatomy and physiology preceding the detailed autopsy findings. Naturally the bulk of the text is devoted to descriptive matter, although the author is careful to avoid too much duplication and shows care in selection according to the importance of the various affections discussed; but most current readers will find their greatest interest attracted to the comments and summaries which the author has widely included, in which he has concentrated his interpretations and comparisons in relation to disease in human beings. The writer would offer as an example the very telling comparison in cardiac pathology between the hearts of birds and those of mammals. Birds naturally have a far higher bulk and weight development of the heart than do animals, their heart-body proportions being often twice that seen in the average mammalian species. But when the heart of a bird is subjected to unusual stress, it has less reserve for compensatory hypertrophy and is more liable to fatal effects. The mammalian heart is far more likely to show evidence of attempted compensation, is more often hypertrophied; and at death to show more signs of having withstood in lifetime all sorts of insults and strains; is more often manifestly and markedly enlarged by hypertrophy, is frequently the seat of "myocarditis" and of muscular degeneration. The writer suspects that the prevalence of arteriosclerosis is greater than is indicated in the Garden records, but the data obtained are at least suggestive, the incidence being highest in the family of hawks and vultures and followed at some distance and nearly alike by the carnivorous animals, the ungulates and the anserines. All four families are characterized by their need for extreme body exertion, thus stressing the mechanical factor of high blood-pressure, and the hawks and carnivores

adding the influence of protein diet. There have been comparatively few aneurysms met in the collection, none of them of the type of the important eroding saccular aneurysms of man; the usual syphilitic factor in the latter being largely replaced in the lower animals by animal parasites inhabiting the interior of the vessels, and both the shape of the aneurysms and the character of the wall differing in consequence. Why is it that the nephritis of animals, quite common among lower mammals, as in the wild rodents, does not more commonly have the usual human accompaniment of arteriosclerosis? Why do these wild animals, in the Philadelphia Gardens living in an industrial city and having a trunk-line railway extending along the longest boundary of the Gardens, have so little pneumokoniosis and virtually never the marked grades found in man? Why is it that the common diffuse atrophic pulmonary emphysema of old human beings and many domestic animals, such as horses, is absent from this collection of wild animals, even though many of the specimens attain what represents senility for them? On the moot point of the influence of biliary entrance into the pancreatic duct in the etiology of pancreatitis, Dr. Fox is able to call attention to the rarity of pancreatitis in birds, which as a class have the biliary and pancreatic ducts well separated (and this rarity in the face of a high incidence of duodenitis); and to a comparative incidence of 14.9 in mammals with proximity or combination of biliary and pancreatic ducts to 13.6 in those with distinct separation of these ducts. This offers some evidence in favor of the belief that bile may at times enter the pancreatic duct and be provocative of pancreatic inflammation. Considerable space is given to an outline of special studies by Dr. E. A. Schumann upon diseases of the female generative organs, represented in the laboratory material and upon questions of comparative obstetrics, the mechanism of labor in the quadrupeds, as illustrated in the Gardens.

As above said it is entirely impracticable to even mention the details of information collected in this volume. The work is in no sense a text-book either upon animal medicine or upon pathological anatomy; it is a work of reference for most students of scientific medicine. One man will be attracted because of the medical aspects of its comparative anatomy; another will find the bacteriological references of the pneumonias encountered of special interest and another the comparative anatomy of the miliary tubercle, as characteristically developed in man, in the bovine, in the monkey, in the bird.

The development of normal comparative anatomy was basic to the establishment of the principles of Darwinism. The broadening of our knowledge of comparative pathology will be found essential for the fixation of any comparable principles of pathology. Books like Bland-Sutton's Evolution and Disease are rare and possible only to men familiar with the sort of material embodied in Fox's

book; and it is as a source book for such information that the present volume is to be regarded. We can whole-heartedly congratulate the author upon the work and can as certainly hope for the appearance of more works of its kind. S.

DIABETES AND ITS TREATMENT BY INSULIN AND DIET. By ORLANDO H. PETTY, M.D., Professor of Diseases of Metabolism in the Graduate School of Medicine, University of Pennsylvania. Pp. 111; 6 illustrations. Philadelphia: F. A. Davis Company, 1924.

DOCTOR PETTY is to be congratulated upon his book on Diabetes, presented as a handbook for the patient. It details in a clear, logical and straight-forward way the subject of diabetes and will be a most valuable adjunct to the physician and to the patient in the handling of the latter's disease. The advice is practical and while here and there are terms and expressions which may be a bit difficult for the lay mind to understand, nevertheless on a whole it is so complete and yet sufficiently elementary that the patient may be able to follow its precepts without very much difficulty. M.

DISEASES OF MIDDLE LIFE. Edited by FRANK A. CRAIG, M.D., Associate Director of the Clinical and Sociological Department of the Henry Phipps Institute of the University of Pennsylvania. Pp. 1871. Philadelphia: F. A. Davis Company, 1923.

THE editor of this monograph states in his preface that the system is compiled "with the object of presenting to the medical profession a series of monographs covering those diseases which are most common during middle life or which have a bearing upon the health, efficiency and well-being of the individual during that important period." He furthermore states that there has been no definite limitation placed upon the period of life which is included under the title of middle life. With this advice in mind the twenty-two collaborators have presented a series of monographs which adhere more or less strictly to the purposes of the volume. They have endeavored, and for the most part successfully, to discuss those disorders which have to do with that epoch in the life cycle in which degenerative diseases begin to manifest themselves. As would be expected in a book of this type considerable space is devoted to diseases of the arteries, kidneys and the heart which preëminently have their onset at least toward middle life. These sections are

most admirable. Doctor Pepper, Doctor Piersol and Doctor Talley are to be congratulated on their presentations. These sections occupy a goodly part of the first volume. The second volume does not apparently carry out as successfully the purposes of the book as does the first volume. Several of the sections are apparently not written with the object of dealing with disorders of middle life but might well be monographs of diseases appearing at any age.

Taken as a unit, the book can be heartily recommended as an exposition of those disorders which are likely to attack an individual when they reach middle life. M.

PRINCIPLES AND PRACTICE OF OBSTETRICS. By JOSEPH B. DE LEE, A.M., M.D. Professor of Obstetrics at the Northwestern Medical School. Fourth edition, thoroughly revised. Pp. 1123; 923 illustrations. Philadelphia and London: W. B. Saunders Company, 1924.

IN every branch of medicine there are two or three text-books which are so far in advance of the average as to be looked upon almost as classics. In this class De Lee's book may be placed without any hesitation. The present edition has been brought up to the minute and naturally such revision has again added slightly to the size of the volume. The author is a conservative teacher who realizes that most obstetric cases are handled by general practitioners and therefore he does not always recommend procedures which only the skilled obstetric specialist can execute. The excellent index is a worthy feature. B.

MEDICAL GYNECOLOGY. By S. WYLLIS BANDLER, M.D., Professor of Gynecology, New York Post-graduate Medical School and Hospital. Fourth Edition. Pp. 930; 157 illustrations. Philadelphia and London: W. B. Saunders Company, 1924.

THE present edition is the first revision in ten years and contains new chapters on urinary diseases, radium, roentgen-ray, constipation and syphilis. Too much space is devoted to endocrinology in view of the present uncertainty in this field and throughout the book there is undue repetition. Many of the subjects are unduly elaborated upon, and it is the belief of the reviewer that if the book were considerably condensed its value would be considerably increased. There is very little in the book which is not well covered by the better general text-books on gynecology. B.

DIE RAUCHENDE FRAU. By R. HOFSTÄTTER, Lecturer on Obstetrics and Gynecology in Vienna. Pp. 266. Vienna and Leipzig: Hölder, Pichler & Tempsky A. G., 1924.

THE author announces this book as a clinical, psychological and social study of the effect of tobacco on women who smoke. The various organs of the female body are considered separately and at length with regard to the injury which can be caused to them by smoking and the effect of tobacco on feminine morals is fully discussed. The author vehemently opposes the use of tobacco by women, especially young women. An extensive bibliography is appended. B.

THE TREATMENT OF THE COMMON DISORDERS OF DIGESTION. A HANDBOOK FOR PHYSICIANS AND STUDENTS. By JOHN L. KANTOR, PH.D., M.D., Chief in Gastrointestinal Diseases, Vanderbilt Clinic, Columbia University; Associate Gastroenterologist and Associate Roentgenologist, Montefiore Hospital for Chronic Diseases, New York City. Pp. 245; 64 illustrations. St. Louis: The C. V. Mosby Company, 1924.

THE reviewer cordially recommends this sane, well written handbook to all physicians interested in the subject. There are excellent chapters on General Principles and Methods, The Management of Functional Digestive Disorders, The Treatment of Ptosis and the Asthenic State, Treatment of the Syndrome of Gastric Irritation, of Gastric and Duodenal Ulcers, of Delayed Gastric Emptying, of Constipation, of Achylia Gastrica, of Gall-bladder Disease, of Diarrheas, and of Headaches Associated with Indigestion. The subject matter is presented clearly and simply and is excellently illustrated. F–H.

HANDBOOK OF MODERN TREATMENT AND MEDICAL FORMULARY. A CONDENSED AND COMPREHENSIVE MANUAL OF PRACTICAL FORMULAS AND GENERAL REMEDIAL MEASURES. Compiled by W. B. CAMPBELL, M.D., Formerly Resident Physician at the Methodist Episcopal Hospital of Philadelphia. Seventh revised and enlarged edition by JOHN C. ROMMEL, M.D. and C. E. HOFFMAN, PH.M. Pp. 693; No illustrations. Philadelphia: F. A. Davis Company, 1924.

SEVEN editions of this book would seem to bespeak some inherent worth, which doubtless lies in the many formulæ that are to be found in it. As a manual of modern medical treatment, however, the book is incomplete and even crude. The first recommendation for

"Appendicitis" is castor oil "to unload the bowels if operation is refused." Diabetes mellitus, according to the authors of this curious volume, "can affect one of normal development as well as can the diabetes produced by brain and pancreas disease." The treatment of meningitis contains no mention of antimeningococcic serum. Seven pages are devoted to syphilis, but not one word is to be found concerning salvarsan and its successors. F.–H.

A Dictionary of Treatment Including Medical and Surgical Therapeutics. By Sir William Whitla, M.D., D.Sc., LL.D., M.P., Emeritus Professor of Materia Medica and Therapeutics in Queen's University, Belfast. Seventh edition. Pp. 1100. New York: Paul B. Hoeber, Inc., 1924.

A monograph upon the treatment of some twelve hundred different pathological conditions in the fields of medicine, surgery and the specialties could hardly be expected to be up to date in all particulars. However, in these pages the reader will find few omissions of importance. The arrangement and treatment of the subject matter is such as to render this a valuable therapeutic reference book for the general practitioner. A.

PROGRESS
OF
MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF
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PROFESSOR OF MEDICINE, JOHNS HOPKINS UNIVERSITY, BALTIMORE, MARYLAND,
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Clinical Studies on Venous Pressure.—EYSTER and MIDDLETON (*Arch. Int. Med.*, 1924, **34**, 228) consider that the taking of the venous pressure in the peripheral veins of a patient at bed rest gives valuable information of beginning cardiac decompensation. Venous pressure rises quite definitely before any other clinical signs of failure are evident. They strongly recommend keeping a close watch on it in cases of pneumonia and other forms of impending decompensation, and to be guided by it in deciding treatment, rather than to wait for other clinical signs. Venesection, while producing only a very transitory effect on the venous pressure in people with normally functioning hearts, cause a rapid fall in the pressure in cases of cardiac decompensation. This fall, too, may be maintained for prolonged periods in such cases, the heart increasing in efficiency as its engorgement is eliminated. Development of valvular lesions in acute rheumatic fever results in alterations of the venous pressure only when cardiac decompensation supervenes. So long as the heart is compensating the pressure remains normal. The anemias, even with the blood viscosity lowered to half, fail greatly to alter the venous pressure.

The Rational Use of Duodenal Drainage.—JONES (*Arch. Int. Med.*, 1924, **34**, 60), in his survey of the results of duodenal analysis in 274 cases, brings out several interesting points regarding the practise of duodenal drainage. Its greatest value, he feels, is its high percentage of definite indications of the presence of gall stones, even when many of his cases were negative as regards history, physical examinations and roentgen-ray findings, the positive signs arrived at from duodenal analysis being confirmed at operation. His analysis consisted mainly

of microscopic examination of the sediment obtained by high speed centrifugation of the drainage samples. In the cases of gall stones characteristic elements were present in the sediment, these consisting of bile-stained epithelium and leukocytes, crystals of cholesterin, bilirubin and calcium bilirubin in abnormal amounts. Any or all of these may be found in either cholecystitis or cholelithiasis, but only in the later disease do the findings exhibit a considerable degree of constancy, especially the large amount of crystalline deposit. The author discounts greatly any deductions made as to the location in the biliary tract of the pathologic changes on the basis of the "A," "B" and "C" bile samples. Also, he criticises the belief that instillations of magnesium sulphate into the duodenum cause gall-bladder contractions and drainage.

Acute Pancreatitis.—EGGERS (*Ann. Surg.*, 1924, **80**, 193), from a careful observation of 6 patients suffering from acute pancreatitis, concludes that the cause of the disease lies in the action of the bile when, and if, it is forced up into the duct of Wirsung. Disease of the gall-bladder was present in all 6 cases, with gall stones in 5 of them while 2 showed a definite jaundice at the time of the attack. Whether normal bile is capable of causing such trouble is questionable, but Eggers points out that the bile here was not normal, since in every case gall-bladder infection had been present. That infection itself is not responsible for the toxicity is proved by several negative cultures from the perotineal fluid in these cases. Eggers believes, then, that abnormal bile, entering the duct of Wirsung, starts the process, and that the subsequent necrosis is most likely due to both bile and pancreatic ferments acting on the surrounding tissues. At one autopsy necrosis was found only around the duct of Wirsung throughout its whole length. The cardinal symptoms of the disease are: (1) Pain, severe, often colicky in character; (2) vomiting; and (3) collapse. Physical examination reveals exquisite tenderness over the pancreas, with little or no rigidity. A polymorphonuclear leukocytosis is usually present. Treatment of the condition is considered to be surgical.

THERAPEUTICS

UNDER THE CHARGE OF

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NEW YORK.

The Therapeutic Use of Digitalis.—The report of the committee appointed by the Council on Pharmacy and Chemistry outlines the limitations of digitalis therapy, and the methods of obtaining digitalis effects. ROBINSON, WHITE, EGGLESTON and HATCHER (*Jour. Am. Med. Assn.*, 1924, **83**, 504) emphasize the dangers of digitalis therapy in partial heart-block, and particularly the intravenous use of digitalis

as an emergency measure in cases of sudden heart failure when a careful study of the heart has been impossible. Such therapy may prove fatal. In auricular fibrillation digitalis therapy is clearly indicated, and though rapid digitalization may be indicated, oral rather than intravenous or intramuscular administration is the method of choice. Digitalis may slow the ventricular action in cases of auricular flutter, and tend to increase the efficiency of the heart. In some cases digitalis may cause a disappearance of extrasystoles, and in cases where digitalis has not been administered their presence is not a contraindication to its use. In cases of complete heart-block the effects of the digitalis bodies on the conducting mechanism of the heart may be disregarded, and their use is not contraindicated. However digitalis should be withheld in cases of temporary block when a return to the normal rate is anticipated. Cases of chronic myocarditis with signs of cardiac failure and normal rhythm will often be greatly improved by digitalis therapy but such cases are often unusually susceptible to the toxic effects of the drug, and oral administration only should be used. Less benefit should be expected from digitalis in cases of aortic insufficiency though valvular lesions do not alter the indications. Only in the exceptional cases where it is imperative that digitalis effects should be obtained in two hours or less is intravenous or intramuscular administration justified, for the body has no way of ridding itself of an overdose when given intravenously or intramuscularly and we do not know how much will be required in any case to produce the desired result. In cases where nausea or vomiting contraindicate oral administration the desired therapeutic effect may be obtained by rectal administration. The total average dose of fairly active standardized digitalis by mouth for inducing full therapeutic effects within thirty-six to forty-eight hours in an adult who has not received digitalis within ten days is about 1.5 gm. of the leaf or 15 cc of the tincture. This may be given in divided doses every four or six hours, or half of the total dose may be given and the remaining half in two divided doses after four to six-hour intervals. If there is doubt about recent medication smaller doses of from 0.1 to 0.3 gm. of the leaf, or from 1 to 3 cc of the tincture should be given three or four times a day. Ambulatory adult patients may be given 0.1 gm. of the leaf or 1 cc of the tincture three times a day by mouth. In an emergency one dose of 0.5 mg. of crystallized ouabain or amorphous strophanthin is enough for intravenous or intramuscular injection, digitalis being given by mouth in doses of 0.3 gm. of the leaf or 3 cc of the tincture every four hours until the desired effect is obtained.

Treatment of Bilharziasis by Antimony Tartrate.—LASBREY and COLEMAN (*Brit. Med. Jour.*, 1924, **1**, 907) explain and summarize the results of their treatment of 4600 cases of bilharzial disease in the Old Cairo Hospital in Egypt by means of sodium antimony tartrate. Intravenous injections of sodium antimony tartrate are thought to be less toxic than the potassium salt. The initial dose is 1 grain increasing ½ grain each injection up to 2½ grains which is the maximum dose. Daily injections for six days are given, then every other day until twelve injections or a total of 27 grains has been given. The full course is given until only "dead" eggs are reported. This method is used for both urinary and rectal cases of bilharziasis, and in the average case

20 to 30 grains is sufficient to effect a cure. Surgical conditions caused by the disease such as papillomata or perineal urinary fistula can be satisfactorily operated on after a preliminary medical course. The mortality among patients taking the course is 4.9 per 1000.

Carbuncle and Its Treatment by Magnesium Sulphate.—MORISON (*Brit. Med. Jour.*, 1924, **1**, 703) reports the successful treatment of 28 cases of carbuncle with a magnesium sulphate paste. The paste is composed of 1.5 pound of dried magnesium sulphate mixed with 11 ounces of glycerine acid carbolic or pure glycerine in a hot mortar and preserved in a covered jar. The paste is applied once or twice a day to the carbuncle, and after a few days the central slough separates leaving a raw granulating ulcer. This is dressed with the paste until healthy granulation tissue appears, then the cavity is packed daily with sterile gauze soaked in a solution of magnesium sulphate made by dissolving 40 ounces of magnesium sulphate in 30 ounces of boiling water and 10 ounces of glycerine and sterilizing in an autoclave. When the healthy granulation tissue is level with the surrounding skin it may be covered with Thiersch skin grafts or allowed to epithelialize. The advantages of this method are: (1) No surgical interference is required; (2) its application is simple and dressings infrequent, once or at most twice a day; (3) the combined osmotic action and its inhibitory effect on the growth and development of the staphylococcus cleanse the wound and assist in the separation of all sloughing and unhealthy tissue; (4) the granulations formed are firm and solid and lend themselves admirably as a base for a superimposed skin graft.

An Antidote for Arsenic, Bismuth, and Mercury Poisoning.—Substantiating the results reported by MCBRIDE and DENNIE (*Arch. Derm. and Syph.*, 1923, **50**, 63) SIMON (*Brit. Med. Jour.*, 1924, **1**, 662) reports 8 cases of metallic poisoning treated by the intravenous administration of sodium thiosulphate and confirms the claims made for this method of treatment in cases of poisoning by arsenic, bismuth, and mercury. Mercury and bismuth stomatitis cases were quickly relieved by three to four intravenous injections of 0.45 to 0.6 gm. of sodium thiosulphate dissolved in 5 cc of water on alternate days.

PEDIATRICS

UNDER THE CHARGE OF

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OF PHILADELPHIA.

The Lange Gold Chlorid Reaction on the Cerebrospinal Fluid in Infants and Young Children.—GRULEE (*Am. Jour. Dis. Child.*, 1924, **28**, 147) found that in congenital syphilis the colloidal-gold reaction in the spinal fluid may assume at times the same degree as that shown in cases of paretic dementia. In this series this occurred twice in cases

of syphilitic meningitis. Congenital syphilis varies rather frequently from the usual reaction that is a fluid which shows the greatest reaction in dilutions of 1 to 40 and 1 to 80. There is no regular agreement between the blood Wassermann and the Wassermann and colloidal-gold reactions in the spinal fluid. There may be a strong reaction both to the Wassermann and to the colloidal-gold solution in the spinal fluid with a negative blood Wassermann. Tuberculous meningitis more nearly conforms to the reaction with greatest intensity in dilutions of 1 to 160 and 1 to 320. It may vary considerably from this in certain cases showing a progressive variation as the meningitis extends. Other conditions which clinically may be easily confused with tuberculous meningitis may show a colloidal-gold reaction not dissimilar from that which is seen in certain cases of tuberculous meningitis. There is no definite reaction in most cases of idiocy and epilepsy.

The Prognosis of Sequelæ of Epidemic Encephalitis in Children. KENNEDY (*Am. Jour. Dis. Child.*, 1924, **28**, 158) studied 61 cases of residual epidemic encephalitis in children under fourteen years of age. Fifty-two of the patients were traced from the time of their first visit until the time of the report; 21, 16 of whom were traced, presented the Parkinsonian syndrome; none were improved; the condition of 2 was stationary and was worse in 14; 1 died from an intercurrent infection. The prognosis in this condition is not bad as regards life, but is poor as regards improvement or recovery. Twenty-three had changes in behavior and personality; 6 were improved, and 17 showed no improvement or had become worse. The lack of restraint exhibited by these children does not necessarily imply any great degree of mental impairment. Nineteen presented disturbances of sleep; 9 of these are now sleeping practically normally; 3 still show more or less disturbance and 7 are the same or worse. The respiratory syndrome occurred in this series much more commonly than is indicated in the literature. Two of the 17 children who had this sequela are well, 3 are improving and the condition of 12 remains unchanged. In a group of 6 children who suffered from the acute illness before the age of four years the after-effects were deplorably severe. One child is well; 5 of the children are mentally deficient as a result of encephalitis; of these 1 is deaf, dumb and blind; 2 are high-grade idiots; 1 suffers from a right hemiplegia, deaf mutism and generalized convulsions of the grand mal type; the other is mentally deficient and has grand mal attacks. In this series the frequency of the disease among the children of lesser years has been fortunately low, as the prognosis in these children is uniformly bad.

The Effect of Pregnancy on the Course of Scurvy in Guinea-pigs.—GERSTENBERGER, CHAMPION and SMITH (*Am. Jour. Dis. Child.*, 1924, **28**, 173) observed that pregnancy modifies both the clinical and pathological picture of scurvy in guinea-pigs. The symptoms accepted at present to be characteristic of advanced scurvy are entirely absent or appear much later, and are much less severe than in non-pregnant guinea-pigs. The daily intake of 5 cc of fresh orange juice supplies the pregnant guinea-pigs, of an average weight of 500 gm., at least as much antiscorbutic material as these animals will consume of their own accord when free to feed on greens. The life term of the pregnant

scorbutic guinea-pig on a proscorbutic diet is on the average the same as that of the controls, even though the clinical and pathological picture of scurvy is mild in the former and severe in the latter. It is suggested that probably the change in the picture of scurvy in the pregnant guinea-pigs is due to the changed metabolic conditions produced by pregnancy, which either raise the resistance of the animal to infections or enable it to economize in the use of antiscorbutic vitamin. It is suggested that even though symptoms of scurvy in the pregnant guinea-pig are milder in degree, the animal's death after parturition is, nevertheless, due to the inadequate intake of the antiscorbutic vitamin.

The Food Requirements of Malnourished Infants with a Note on the Use of Insulin.—MARRIOTT (*Jour. Am. Med. Assn.*, 1924, **83**, 600) points out that some infants fail to gain even when the nutritional requirements have all been met. In these infants it is necessary to resort to means for increasing the capacity of the infant for utilizing food. The most effective means in his experience has been transfusion. He gives such infants repeated transfusions of matched citrated blood. The amount given at a transfusion is about 1 ounce of blood for each 3 pounds of body weight. Very often an infant will begin to gain following transfusion, although the feeding is not changed. Besides oral methods of administering foods, the intravenous method may be used. Glucose can be given intravenously in a 20 per cent solution provided the injection is given slowly. The amount of the injection should be from $\frac{1}{3}$ to $\frac{1}{2}$ ounce of 20 per cent solution per pound of body weight. Glucose given in this way is only partly utilized, but if insulin is given at the same time better utilization of the sugar occurs, and a gain in weight of the infant is the result. Insulin is used in those cases because of the observation that diabetic patients on insulin treatment often gain in weight at a phenomenal rate, even when the food intake is not excessive. There would seem to be a good explanation for this observed fact. Marriott found that the best results were obtained when considerable amounts were given. He recommends the use of a 20 per cent solution of glucose containing 15 units of insulin per 100 cc. Such a solution has sufficient glucose to completely act as a buffer to the insulin. No bad results were observed. The injections may be given daily over an extended period. He found the results uniformly successful. A gain in weight nearly always occurs, even in cases where infection is present. The weight gained is not subsequently lost when the injections are finally discontinued. Marriott has not used this procedure routinely but has confined its use to the most extreme cases of athrepsia.

Intestinal Obstruction in Children.—LADD and CUTLER (*Boston Med. and Surg. Jour.*, 1924, **191**, 141) analyzed 88 cases of intussusception and 17 cases of obstruction from other causes. The youngest patient was three weeks old and the oldest was almost nine years of age; 66 patients were under one year of age; 2 cases of intussusception occurred as a sequel of appendectomy (1 of these occurred before the patient was discharged from the hospital, and the other two or three days after his discharge); 1 case occurred during an attack of diarrhea and 1 case followed purpura. In patients in whom the invaginated

bowel had not become so swollen and edematous that it could not be reduced the mortality was high but not excessive. In this series there were 72 such patients operated on; 14 patients died and 58 recovered, a mortality of 19.4 per cent. Among the remaining patients on whom resection or enterostomy was performed the mortality was very high. Of 9 cases in which resection and lateral anastomosis was performed 8 died. The 17 cases in which obstruction was due to other causes than intussusception there were 3 which were subsequent to operation for intussusception; 2 cases were the result of Meckel's diverticulum becoming adherent across the ileum; 1 child died and 1 recovered; 3 children had obstruction during the first ten days of convalescence following operation for appendicitis with peritonitis; 3 cases, developed months after appendectomies with drainage, recovered by freeing the bands of adhesions; in 1 patient, from whom an enormous mesenteric cyst had been removed, obstruction resulted from a combination of narrowing the lumen of the bowel and adhesion of the appendix to the site of excision; there was 1 case of strangulation of a loop of ileum through a defect in the mesentery. In these 17 cases of obstruction from varied causes enterostomy was performed 6 times with successful outcomes in 5 instances.

Intracranial Hemorrhage in the Newborn.—Sharpe and Maclaire (*Am. Jour. Obst. and Gynec.*, 1924, **8**, 172) found that in 100 consecutive deliveries that 10 per cent of the babies showed in the spinal fluid evidences of intracranial trauma. In 4 cases the cerebrospinal fluid was bloody, and in 6 cases it was yellow, in only 4 of which it was possible to demonstrate red blood cells. The yellow spinal fluid of newborn infants is probably the result of transudation of the blood plasma when red blood corpuscles are absent, and due to minute hemorrhages when red blood corpuscles are present. Of 4 cases of icterus neonatorum in this series only 1 had yellow spinal fluid. Early lumbar puncture is advocated in the absence of shock, not only for its diagnostic value, but also for its therapeutic value in early cases of cerebral hemorrhage and cerebral edema. Repeated spinal drainage at least every twelve or twenty-four hours is indicated, dependent on the size of the extravasation or the amount of cerebral edema as indicated on the spinal manometer. A modified subtemporal decompression and cranial drainage should be advocated only when the lumbar puncture drainage fails.

DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF

JOHN H. STOKES, M.D.,

PROFESSOR OF DERMATOLOGY AND SYPHILOLOGY AT THE SCHOOL OF MEDICINE, UNIVERSITY OF PENNSYLVANIA.

Dermatoses Due to Cosmetics.—Cole (*Jour. Am. Med. Assn.*, 1924, **82**, 1909) discusses in a brief summary the enormous increase in the use of cosmetics, and the dermatoses definitely attributable to

scorbutic guinea-pig on a proscorbutic diet is on the average the same as that of the controls, even though the clinical and pathological picture of scurvy is mild in the former and severe in the latter. It is suggested that probably the change in the picture of scurvy in the pregnant guinea-pigs is due to the changed metabolic conditions produced by pregnancy, which either raise the resistance of the animal to infections or enable it to economize in the use of antiscorbutic vitamin. It is suggested that even though symptoms of scurvy in the pregnant guinea-pig are milder in degree, the animal's death after parturition is, nevertheless, due to the inadequate intake of the antiscorbutic vitamin.

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Dermatoses Due to Cosmetics.—Cole (*Jour. Am. Med. Assn.*, 1924, **82**, 1909) discusses in a brief summary the enormous increase in the use of cosmetics, and the dermatoses definitely attributable to

them. He classifies the reactions produced under the head of the poisonous drugs contained in the preparations. Dermatitis from hair dyes containing as high as 23 per cent lead acetate and lead carbonate or "flake white" used in face enamels to give them a soft feel, and cases of lead line, lead palsy and gastrointestinal disturbances due to lead carbonate or flake white, are among the most important and serious intoxications. Mercurials are responsible for pigmentation, as in the pigmentation reported by Goeckerman as due to calomel in face creams, and for dermatitis from mercuric chlorid in bleaches, in which the drug is found sometimes in a concentration of 1 to 200. Most so-called "rice powders" contain no rice, and do contain large amounts of bismuth, responsible for occasional poisonings. Severe dermatitis with swelling of the eyelids is reported from the use of a hair tonic containing 1.06 grains of arsenious acid to the fluidounce. Wood alcohol was shown by Newcomb to be present in 20 of 66 toilet preparations examined. Mild and occasionally severe dermatitis is produced by depilatories. Paraphenylenediamin is one of the most grossly abused and common of the dermatitis-producing drugs. It is a common ingredient in hair and fur dyes, and produces a remarkably severe and intractable dermatitis. From February 13 to September 4, 1909, 32 cases were reported to the American Medical Association alone. France Germany and Austria have prohibited the use of this drug entirely. Oxidation with hydrogen peroxid stops the action of the dye, but does not necessarily protect against the dermatitis. It has recently been marketed as an ingredient of eyebrow paints. The author has also seen examples of dermatitis of the face and neck traceable to the preparations now in use for sleeking down the hair.

Bilirubinemia in Patients Treated with Arsphenamin.—SCHAMBERG and BROWN (*Jour. Am. Med. Assn.*, 1924, **82**, 1911) report a series of studies of the bilirubin content of the blood in patients under treatment with arsphenamin. They find in confirmation of the findings of Chargin and Orgel, and of Greenbaum, that a bilirubinemia may follow the administration of the arsphenamin, but that it has no relation to the number of injections of the drug administered, and is apparently a matter of individual idiosyncrasy. They believe the van den Bergh method to be of practical value in determining the latent jaundice of patients under treatment, and note that it is preferable to examinations for bilirubenuria. MacCormack and Dodds (*British Med. Jour.*, 1923, **1**, 1200) found that liver reserve is so great that the ordinary course of 8.7 gm. of neoarsphenamin has no significant damaging effects.

Hexamethylene Dermatitis in the Rubber Industry.—CRONIN (*Jour. Am. Med. Assn.*, 1924, **83**, 251) reports an occupational dermatitis affecting 60 workers in a rubber factory, which was traced to hexamethylene which is used as a catalyzer in the vulcanization of rubber. The amount of the drug did not exceed 1 or 2 ounces in 100 pounds of rubber stock, yet severe and intractable cases were traced to the heel room where rubber heels were removed from the hot vulcanizing presses, and continued to appear for many weeks sporadically as the scrap rubber containing the drug was used up, even after the main supply had been cut off. As is usual in epidemic occupational derma-

toses, an infectious factor made itself manifest in the form of furuncles and abscesses in the affected workers. Local applications were not successful in controlling the situation. The itching of the dermatitis of arms and face was a conspicuous symptom.

Chlorid Retention in Pemphigus.—KARTAMISCHEW (*Arch. f. Dermat. u. Syph.*, 1924, **146**, 235) maintains that chlorid retention with marked reduction of sodium chlorid in the urine, when associated with eosinophilia, is a valuable aid in the diagnosis of malignant pemphigus, especially at the stage when only mouth lesions are present. The electrical resistance of the skin in this disease is normal.

Action of Silver Arsphenamin.—The following table which appears in a review in the *British Journal of Dermatology* (1924, p. 130) of an article by SATKE (*Dermat. Ztschr.*, 1923, p. 349) deserves reproduction in view of the scarcity of tangible data on the actual comparative efficiency of the arsphenamins which are on the market today. The author is quoted as considering silver arsphenamin as an effective drug for the removal of clinical signs of syphilis but as inferior to original arsphenamin and mercury treatment in permanence of results. He observed 2 cases of argyria after total doses of 15 and 16 gm.

Silver Arsphenamin.

	No. cases.	Cases followed.	Clinical relapse.	Serum relapse.	C. S. F. relapse.	Resistant W.R.	Dermatitis.
Abortive cases W. R. negative at start	15	8	4	1			
Preventive cases	15	5	2	..	1	3	1
Secondary cases	53	22	11	5	5	11	3
Latent cases	17	4	..	4	..	2	2
Lues malignat	1	1	..	1			

Arsphenamin-mercury.

Abortive cases W. R. negative at start	15	8	..	1			
Preventive cases	15	5	..	2			
Secondary cases	53	22	2	4	2	6	1
Latent cases	18	4					
Lues malignat	1	1					

The patients were all young women between the ages of fifteen and thirty years, and the two series were as nearly comparable as is reasonably possible.

OBSTETRICS

UNDER THE CHARGE OF

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Natural Imunization in the Newborn.—MUSSELMAN (*Am. Jour. Obst.*, July, 1924) gives the results of his observations on this subject in the Department of Obstetrics in the Yale School of Medicine. He

found that with one exception only, in all his experience, the maternal serum had a higher value in producing immunity than the serum of the newborn. In some cases the serum of the infant failed to show any appreciable quantity of immunizing bodies; others have found that the newborn is independent of the mother for its antibodies. In examining infants prematurely born of mothers suffering from typhoid fever agglutinins were absent. Child born during the typhoid infection of the mother had a lesser immunizing value than those born of mothers who had typhoid fever just before pregnancy. When animals were immunized against typhoid and cholera during pregnancy, they gave birth to young having less agglutinin than the mother. Children born of tuberculous women usually showed some antibody in the blood stream. The content of bacteriolysins is higher in maternal serum than that of the newborn. The serum of the human mother possess a higher content of hemolysin than the serum of the child, which in many cases fails to show any appreciable quantity. So far as opsonins are concerned, the maternal and fetal serum seems of equal value, both diminish during the first days of life and increase spontaneously; in precipitins the maternal serum was always higher than that of the child. The antiferment action of the mother's blood is greater than that of the newborn. It is difficult to harmonize all the findings reported by various investigators, it may be that placental transmission of antibodies depends upon the type of placentation, but it is interesting to note that from our clinical experience we find that if the mother has developed an infection such as typhoid fever or smallpox in the latter months of pregnancy, the child is more likely to show infection than if the disease had occurred in the early months of gestation.

Syphilis as a Complication of Pregnancy in the Negro.—Bartholomew (*Jour. Am. Med. Assn.*, July 19, 1924) analyzes his results in the study of 300 cases of syphilis in negro women. He describes 5 cases in which the symptoms varied so greatly that a diagnosis was difficult. He is accustomed to study his cases by a roentgen-ray examination of the fetal bones, microscopic examination of the placenta and a dark-field examination of material aspirated from the fetal liver. By this latter method he frequently detects spirochetes. In comparing the pregnancies of 100 non-syphilitic and 100 syphilitic patients without treatment and 100 syphilitic patients who received treatment, in a clinic where at least one-third of the patients are syphilitic, the syphilitic patients showed three times as many abortions and premature labors and seventeen times as many stillbirths as did those who were not syphilitic. Among those patients receiving treatment before labor, the number of premature births was reduced one-half; there were one-third as many stillbirths; one-seventh as many abortions and one-ninth as many infant deaths up to ten days as in those patients who received no treatment. The treatment employed was the giving of 1.14 gm. of arsphenamin and 0.04 gm. of mercuric salicylate, from seven months on to term. He believes that a dark-field examination on a suspension of liver tissue obtained at autopsy or aspirated from the liver is a valuable aid in diagnosticating syphilis in the infant. Its results agreed with the maternal Wassermann reaction in 70 per cent of the cases.

The Care of Patients in Private Practice and the Physician's Responsibility.—At a recent meeting of the British Medical Association (*Brit. Med. Jour.*, August 16, 1924) in discussing the value of antenatal care, MacKenzie stated that a physician is not justified in accepting service for a confinement if the size of his practice, his other occupations or the state of health are to be made an excuse for his failure to carry out those measures of antenatal care, attendance during the actual confinement and postnatal watchfulness which are in accordance with modern knowledge and hospital practice. He considers the responsibility of maternity practice greater than any other assumed by a physician. His practice has averaged 3700 visits and 2400 consultations yearly with 11,200 miles of traveling. The average number of confinements yearly has been 77, a third of whom were primiparæ. His patients are the families of fishermen, farm laborers and cottagers. In very few houses are there conveniences of any kind and water is brought from outside wells or pumps. Under these conditions he has tried to carry out antenatal care and modern practice. When engaged for a confinement he visits his patient, makes an examination thoroughly and instructs the patient carefully about the hygiene of pregnancy. He leaves with her a printed pamphlet and insists that samples of urine be sent regularly. He again sees his patient about the fifth month, confirming his estimate of the period of pregnancy, measuring the pelvis and repeating his general examination. He explains the preparation for confinement and inspects the bed which the patient proposes to use. His last visit before confinement is a week before the expected time. Examination is repeated and especially to ascertain the presence or absence of descent and engagement. The success of this method has been to physician and patient most gratifying. In 680 confinements of which 224 were primiparæ, there has been no maternal death or infection and 11 stillborn children. Of these 3 were monsters; 2 had spinæ bifida; there were 3 cases of eclampsia and 4 cases of antenatal albuminuria. Labor was premature in 13 and the placenta had to be removed manually in 14. The forceps was used in 212 cases and in 151 the perineum was repaired. Eighteen breech presentations and 4 shoulder presentation were included. His preparation for actual confinement is thorough cleanliness, the emptying of the patient's bowels and bladder and an efficient nurse in attendance. Lysol, a pound package of cotton and two deep basins are provided. The bed is supported by boards slipped under the mattress which is covered with thick brown paper or water-proof sheeting. When labor starts a dose of castor oil is taken followed by a copious enema. With these simple methods his practice has been satisfactory to his patients and to himself.

Maternity Work Among Soldiers' Wives.—Moss (*Brit. Med. Jour.*, August 16, 1924) reports his results in attending confinements among soldiers' wives in the hospital at Aldershot. There were 1850 cases and only 4 who had not attended the antenatal clinic. Among those who had received antenatal care, there was 1 death from pulmonary embolus on the seventh day which followed septic infection in a case of perineal laceration and forceps delivery. If officers' wives are included; there were over 2000 confinements with 1 death among those who received antenatal care. There were 2 deaths of patients admitted

in a dying condition, 1 from advanced disease of the heart, the other from antepartum bleeding. There was no difficulty in conducting antepartum examinations or care, as patients welcomed such attention. Among the cases were 8 Cesarean sections, 2 for placenta previa, 1 for tumor in the cervix and 1 for fibroid in the uterine wall. The others were for contracted pelvis. Three cases of eclampsia with fits recovered. Several women had threatening symptoms, but did well with care. The forceps was used in about 7 per cent of the cases. The writer is especially impressed with the value of external version. This he performed in 54 cases of breech presentation without using anesthesia. He recognizes the fact that this manipulation may cause accidental hemorrhage by a separation of the placenta. In 3 cases the fetal legs were extended and version failed. One case where the fetus weighed 24 pounds, was mistaken for twins. The child was delivered stillborn and the mother had some laceration. In the last four years there were no cases of sepsis. Before that there were 3 cases where the blood was sterile, but the discharge from the genital tract contained bacteria These recovered after treatment by swabbing out the uterine cavity with 1 to 500 acriflavine solution. The writer lays stress upon examining the outlet of the pelvis in all patients pregnant for the first time. His antenatal equipment consists of a pelvimeter, stethoscope, urine-testing outfit, blood-pressure outfit and rubber gloves. In discussion upon the general subject of antenatal care, Adamson, of Leeds, spoke of experience in 4958 patients in private practice and among those working in factories during the recent war. Among the factory workers, there were 40 confinements with an average of 39 living children. Some of these women had difficult and unsuccessful labors previously. It was customary in these cases to examine the vaginal secretion and also to make a Wassermann test of the blood. Among the hospital population of Leeds rickets is not uncommon. Cesarean section is often necessary. The toxemia of pregnancy is very common and many cases are brought in neglected and in serious condition. Placenta previa is common and these cases frequently are neglected in the early stages. The type of syphilis seen among these patients was mild. Bourne urged that hemorrhage before labor in late pregnancy where the presenting part is not engaged should be regarded as placenta previa and pregnancy ended as soon as possible. Where the head was engaged, if the patient had albuminuria or edema, the treatment should be rest, dieting and sedatives. Johnstone of Edinburgh recalled Ballantyne's work in this connection. To illustrate its success, he reported 58 cases of albuminuria admitted for treatment of whom only one developed eclamptic fits. He thought pelvimetry valuable and employed vaginal examinations to measure the outer conjugate. To bring on labor he used quinin, castor oil and pituitrin. If this method failed, he used bougies. Others drew attention to the fact that vaginal examinations can be safely omitted in most cases and that regulation of diet can be employed where in previous pregnancies the child has been overdeveloped. The value of antenatal clinics and staffs was illustrated by the reports of five hundred and fifty of these clinics. The trend of the papers and discussions was to emphasize the value of antenatal care in connection with hospital confinements. Antenatal clinics should be in charge of obstetric specialists and those who have had considerable experience.

The Value of Blood Chemistry in Pregnancy.—From the laboratories of the Naval Medical School at Washington, BUNKER and MENDELL (*Jour. Am. Med. Assn.*, September 13, 1924) report studies in the blood chemistry in pregnancy in 52 patients. Between the second and third months there were only six tests made, but for each of the succeeding months there were from nine to twenty. A chart is given of the monthly average of a normal fetal growth showing the various elements in excretion. A detailed table is also published giving the findings in normal cases. The writers have found variations in considerable quantity among many of the patients observed. In normal cases the curves of uric acid and cholesterol are almost parallel. This latter substance possesses antitoxic properties, so that its presence is a preventative, quite counter-balancing the toxicity produced by uric acid. From this a practical application suggests itself, that a diet rich in cholesterol during the latter part of pregnancy would be advisable, especially in cases showing a tendency to toxemia. Experiments made in the production of cholesterol by certain fats show that cream, butter, mushrooms, egg-yolks, alligator pears, oatmeal, salmon, black bass, olive oil, cod-liver oil and other fats increase the quantity of cholesterol. The last reading in these substances was in a patient at six months who subsequently had a long labor, developed sepsis and made a tedious and complicated recovery. The pathologic cases comprise 17, varying from mild toxemia to convulsions with coma. There were 5 cases of eclampsia in which the chemical examination of the blood gave findings within normal bounds. A follow-up report shows that these patients had no kidney improvement on their recovery. In 1 case admitted at term in convulsions, blood was obtained within less than one hour of a convulsion. Mother and child recovered and subsequently went through normal pregnancy and labor. In a subsequent pregnancy she was admitted again to hospital at eight months in convulsions with normal blood findings. The patient died. At autopsy the pathologist reported the liver changes typical, with acute terminal nephritis. In the nephritic toxemia blood chemistry showed nitrogenous retention of varying degree and in these cases a kidney lesion persisted to some extent. Nephritic cases with high blood-pressure showed retention of nitrogen with high uric-acid content. In the nephritic cases the cholesterol values are uniformly high. When the average findings in these cases are studied, it is interesting to observe how little difference there is between charts of normal cases and eclampsia, and what a wide difference there is between eclampsia and nephritic toxemia. Where eclampsia was pronounced the blood chemistry was practically normal. Where toxemia was the important feature without convulsions, there was decided nitrogen retention. On this finding the writers divide their cases of toxemia into eclamptic and nephritic toxemia. They realize that their number of cases is comparatively small, but they believe that the results are of wide interest. The reviewer would call attention to the fact that it has long been recognized that eclamptic convulsions are a conservative process and tend—if they are not in excess—toward the patient's recovery. Convulsions cause relaxation of the bloodvessels, often perspiration, a discharge of urine and feces and frequently bring about labor. The fact that patients sometimes recover after many convulsions and others die quickly who have none illustrates these facts.

GYNECOLOGY

UNDER THE CHARGE OF

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Surgical Treatment of Uterine Prolapse.—The operative treatment of uterine prolapse has always been far from standardized, and the results of any method of treatment have all too frequently been discouraging. Some men are most enthusiastic about a certain operation, perhaps their own invention, while others will almost swear by an operation based upon entirely different principles and yet both groups will have some good results and also some very poor ones if they take the trouble to follow their cases over a period of a few years. Under these circumstances there should be some value in obtaining the opinion and advice of a man who has had many years' training in gynecological surgery and has tried many of the numerous operations devised for the cure of this distressing condition. Such a man is MEYER (*Med. Jour. Australia*, 1924, **1**, suppl. 177), who is consulting surgeon to the Women's Hospital in Melbourne. If the patient is in the child-bearing period the first object is to restore the uterus to its normal position, to maintain its natural freedom of motion, to repair all weakness and injury of the pelvic floor; in other words, to restore conditions for a favorable pregnancy and delivery. In the first degree of descent which has followed on childbirth there has been injury to the perineum, more or less stretching and tearing of the levator ani muscles, the recto-vaginal and vesicovaginal fasciæ. Perineorrhaphy with strengthening of the anal sphincter and anterior colporrhaphy are essential in every case. Even with a very small cystocele it is wise to anticipate an increase and to correct it. In a considerable proportion of cases with a moderate degree of descent of the uterus colpoperineorrhaphy and anterior colporrhaphy will give the uterus back its natural support and preserve its fitness for childbirth. If there is a tendency to backward displacement the reconstruction of the pelvic floor will in most cases correct that tendency. When there is any doubt about the matter the author makes a small abdominal incision and plicates the round ligaments. He has given up the Alexander operation after a long experience with it. In the second degree of prolapse, after repair of the pelvic floor, if the round ligaments are firm and allow of a fair length of shortening, he performs anterior plication; one fold of each ligament is fastened to the anterior surface of the uterus and the two ends of the free loops are sutured together, thus combining a forward and a suspensory pull. His second choice in this type of case is the Gilliam operation. Its simplicity appeals to him, but he has never

quite satisfied himself that the pregnant uterus under the altered condition of the pull of the implanted round ligaments could be relied on to maintain the normal anteposition which makes for normal delivery, and he believes that occipitoposterior positions occur frequently after this operation. In cases of third degree prolapse (procidentia), where the broad ligaments are nearly always relaxed from the long-existing drag, an excellent result is obtained by taking in the slack of each broad ligament and folding it posteriorly to the posterior surface of the uterus. The operation is very simple, the chief point to observe being the avoidance of the ovarian vessels, below which the sutures into the ligaments make their initial pass. Along with this a simple single surface to surface fold of the round ligament completes a measure which gives both elevation and direction to the uterus. After the menopause, unless some chronically enlarged or degenerate prolapsed uterus makes hysterectomy imperative, the author does a wide anterior and posterior colporrhaphy and perineorrhaphy supplementing it with either a Gilliam operation or a ventrofixation. In the event of a supravaginal hysterectomy the cervical stump is sutured to the ends of the broad ligaments.

High Voltage Roentgen Therapy of Cancer.—The new high voltage method of applying the roentgen-ray to cases of uterine cancer, which was introduced in Germany a few years ago was heralded as a very distinct advance in this field and was quickly followed by the roentgenologists in this country. Sufficient time has now elapsed since the introduction of this method for some definite statement as to whether it has proved to be all that it was heralded. It is of very great interest therefore to review an article by HERLY (*Jour. Radiol.*, 1924, **5**, 71) based upon his personal observations and experiences during an extensive recent tour of most of the European medical centers and in which he quotes the views of many of the leaders in this field. He emphasizes that roentgen-rays do not directly kill the cancer cells, but they have a destructive action on all cells and when intensive radiation is given it will damage connective tissue, which must be regarded as a barrier to the cancer cell, and injury to it opens a breach in the protective wall, allowing an invasion of the cancer cells that are left unaffected by the rays. Since carcinomas are of different types and degrees of malignancy, not always distinguishable by the microscope, how can the same method of treatment and the same dose produce curative effects in all cases? Therefore a standard "carcinoma dose" of roentgen-rays cannot be established biologically. There is no unimpeachable proof that insufficient raying stimulates tumor growth. From the evidence at hand, the author states that there seems to be no reason why the old machines, as commonly used in this country for therapy, with increased distance, filtration and time, will not produce as good results as the high voltage apparatus introduced by the Germans. Intensive high voltage raying damages the normal tissues and damage to the endocrine glands reduces the general resistance of the patient and by itself even may lead to death. The condition of the organism in general cannot be neglected in seeking indications for roentgen-ray theraphy, and it should be remembered that undernourished and cachectic individuals are roentgen-refractory.

Treatment of Chronic Gonorrhea in the Female. — Any logical method of treatment of chronic gonorrhea in the female necessitates the removal of the infection from the cervix, Bartholin's glands and Skene's glands. Since we are dealing with complicated glandular tissues, SHUTTER (*Wisconsin Med. Jour.*, 1924, **23**, 69) believes that this can be best accomplished by their destruction with the cautery. In the case of the cervix this is usually done without anesthesia by the introduction of a small nasal cautery tip as far upward as the internal os. The current is connected and the tip drawn outward to the external os. If the vaginal mucosa is not touched by the heated instrument almost no pain is felt. One or two linear cauterizations are made and the operation is repeated several times at intervals of about two weeks. Erosions and Nabothian cysts respond readily to cautery applications. All patients are advised to keep the cervical secretions removed by the use of a daily douche. Moderate hemorrhage following cauterization is not infrequent and patients should be reassured against alarm. Novocain infiltration of the surrounding tissues is necessary before cautery destruction of the paraurethral glands, using a 2 per cent solution. The ducts are exposed with hair-pin probes and the fine cautery tip is then placed on the floor of the urethra and the ducts laid open throughout their entire length. While cautery destruction of the Bartholin glands and ducts is not difficult under local anesthesia, the area remains painful and tender for some time. Excision of the entire structure with the knife is simple, more effective and the postoperative course more satisfactory. The above routine has been more satisfactory to the author than any other measures previously employed. Chronic cases have yielded continued negative smears after from three to ten weeks. Where results have been poor careful reëxamination of the three possible foci has usually revealed the bacterial source. In several cases it has been impossible to obtain negative smears from the cervix because of the coexistence of chronic tubal infection. All patients are advised to remain quiet during the menstrual periods following cauterization, and because of the danger of extension of the disease treatment has seemed inadvisable for two or three days before and after menstruation.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

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Deaths among Taxpayers and Non-taxpayers of Income Tax, Providence, 1865.—CHAPIN (*Am. Jour. Pub. Health*, 1924, **14**, 647) states that in a city of over 50,000, in 1865, the death-rate in the families

of income taxpayers was less than one-half what it was among the non-taxpayers. This was not due to difference in age distribution nor to parent nativity. Though the figures for different causes are too small to warrant definite conclusions, or to permit further detailed study, they are certainly suggestive and warrant further investigation along these lines. However, one uncertainty common to such studies is minimized. An income tax seems to be a far better means of segregating persons of good economic status than do geographical distribution, number of servants or number of rooms in the house. When we have definitely determined the incidence of different causes of death on the two classes we will be prepared for what should be of great value, namely a study of the habits of life and of the environment which make for the longevity of the well-to-do.

Results in the Treatment of Congenital Syphilis.—FORDYCE and ROSEN (*Arch. Dermat. and Syph.*, 1924, **9**, 355) have studied the results of prenatal treatment upon congenital syphilis. They have learned to be guarded in their opinion of the results of the Wassermann test on the blood from the umbilical cord. A long period of observation has shown that a positive Wassermann reaction at the time of delivery is not always evidence of syphilis in the infant, nor is the negative an indication that the child has escaped the infection. In the absence of clinical signs of the disease greater reliance should be placed on routine tests taken a week or ten days after birth, and thereafter every four weeks up to the age of six months. The interval may be lengthened to three months until the infant is two years of age, after which time an effort should be made to keep the child under observation for semiannual examinations for an indefinite period. If, at the end of two years the child has continued to have negative reactions in the blood and the spinal fluid, and is negative clinically, in all probability it is free from syphilis. The success of prenatal treatment depends on the duration of the infection, early administration of treatment and the amount tolerated. Microscopical examination of the placenta may prove of greater value in determining a latent infection than the result of the Wassermann reaction on the blood from the umbilical cord or from the veins during the early months of life. Occasionally cases of active syphilis with a negative serology are seen. Clinical manifestations must always take precedence over laboratory findings. The prognosis of congenital syphilis depends on the amount of prenatal treatment, the physical condition at birth, the severity of the infection, whether visceral, cutaneous or neural involvement is present, the time treatment is begun, the type of treatment and the toleration to treatment.

The Cause of Foot-and-mouth Disease.—A rare example of a reward for steadfast concentration on one problem by one man is to hand in the news that the virus of foot-and-mouth disease has at last been isolated by PROF. PAUL FROSCH, Professor of Dietetics and Bacteriology in the Konigliche Tierarztliche Hochschule in Berlin, working in conjunction with PROFESSOR DAHMER (*Lancet*, 1924, **206**, 962). More than twenty years ago the author, working with Löeffler (*Jour. Comp.*

Pathol., 1899, **12**, 79) discovered that a filtrable virus was responsible for foot-and-mouth disease. The author has worked at this subject with persistent diligence ever since, and at a meeting of the Berlin Microbiological Society, April 7, 1924, he was enabled to announce the discovery of a tiny bacillus which he has isolated and from which he has been able to reproduce the disease after thirteen subcultures. The organism is only 0.1 micron long in suitable solid medium, of the diameter of a red blood corpuscle, that is, 7 to 8 microns. This bacillus the two workers generously propose to name *Löeffleria nevermanni*.

The Soluble Specific Substance of Pneumococcus—HEIDELBERGER and AVERY (*Jour. Exper. Med.*, 1924, **40**, 301) have improved the method for the concentration and purification of the soluble specific substance of pneumococcus. Highly purified specific substance of Type II pneumococcus of polysaccharide nature was recovered essentially unchanged after precipitation by immune serum, by uranyl nitrate, by basic lead acetate or by safranine. Marked chemical differences exist between the specific substances of Type II and Type III pneumococcus, although both react as polysaccharides. The weight of evidence is considered to be in favor of the view that the specific substances of pneumococcus Types II and III are actually polysaccharide. The authors discuss the immunological significance of the foregoing view.

The Catalytic Action of Minute Amounts of Copper in the Destruction of Antiscorbutic Vitamin in Milk.—HESS and WEINSTOCK (*Jour. Am. Med. Assn.*, 1924, **82**, 952) state that the antiscorbutic vitamin is readily destroyed by oxidation, especially when the oxidative process takes place in association with heat. This sensitiveness leads to a partial loss of this factor in the process of pasteurization. The gradual decrease of vitamin in the course of the "aging" of foodstuffs, such as vegetables, is to be interpreted in this way. Catalysis greatly increases the velocity of oxidation and thus furthers the destruction of this vitamin. A series of animal experiments demonstrated that when as little as 2.5 mg. of copper per liter, 2.5 parts per 1,000,000, were added to milk the antiscorbutic vitamin was appreciably reduced in the course of heating. Although copper does not go into solution to this extent in the course of well-supervised pasteurization, such contamination readily occurs when the equipment is not in good repair or well cared for. The risk is still greater in the process of condensing milk. A similar danger exists with regard to the contamination of butter and cream. The importance of copper in relation to these dairy products lies in the fact that we are largely dependent on them for our quota of the fat-soluble (vitamin A), and that this vitamin is also highly sensitive to the destructive action of oxidation. The circumstances may be the same in relation to other foodstuffs rich in one or both of these nutritional factors, for example, the green vegetables. At present contaminations of food with copper or other metals are judged by the standards of toxicology. This criterion is manifestly inadequate, for even non-toxic traces of these substances suffice to bring about the catalytic destruction of the vitamins.

Deaths and Disabilities from Heart Disease.—HEFFRON (*Am. Jour. Pub. Health*, 1924, **14**, 652) states that heart disease causes more deaths and more disability than any other disease. Heart disease is due to an infection. Infections are more easily contracted by exposure when in a condition of undernourishment, or of fatigue, or when resistance is lowered by an unduly prolonged spell of cold or of hot weather. The danger of infection is greatest in children. Many of the infections which cause heart disease enter the blood stream from diseased tissues in the mouth and nose. All diseased tissues in the mouth can be removed without danger and without damage to the general health, and with marked improvement and increased safety. All infections should be avoided by avoiding contact with the sick or by active immunization. Heart disease does not always show itself by symptoms which call attention to the heart. Attention to the details of personal hygiene is a protection against heart disease. No person knows whether he is sound or not without frequent health examinations.

Recent Investigations of Absorption and Excretion of Lead in the Organism.—AUB, MINOT, FAIRHALL and REZNIKOFF (*Jour. Am. Med. Assn.*, 1924, **83**, 588) say that lead is absorbed more rapidly through the whole respiratory tract than through the gastrointestinal tract. It is carried in the blood stream as a phosphate. Lead is stored in the calcareous portion of the bones. Damage results only when lead is being transported after absorption or following release from the bones. In active plumbism lead is distributed more widely through the body than in the chronic inactive form of the intoxication. The administration of acids or alkalis, particularly when associated with a low calcium intake, accelerates the release of lead and its excretion. A positive calcium balance in the body favors retention of lead in the bones.

Persistence of Inspired Bacteria in the Lungs of Alcoholized Mice.—STILLMAN (*Jour. Exper. Med.*, 1924, **40**, 353) states that when mice are exposed to an atmosphere containing certain bacteria in the form of a fine mist, the bacteria may be recovered from the deeper respiratory passages. Pneumococci which have reached the lungs of normal mice as a result of this procedure usually disappear within a few hours and give rise to no generalized infection. In mice intoxicated with alcohol, on the other hand, pneumococci persist in the lungs for a longer period and fatal septicemia frequently follows. Hemolytic streptococci and Bacillus influenzæ generally persist in the lungs for about twenty-four hours. In intoxicated mice these organisms do not disappear so rapidly from the lungs and generalized infection is much more frequent. The experiments yield no evidence as to how alcoholic intoxication renders the lungs more permeable to inspired bacteria.

Typhoid Fever and Ice.—Owing to the fact that ice purifies itself in the process of freezing, typhoid fever has rarely been traced to the ice supply. In fact, very few instances are on record in which ice has been accused, and in these instances the evidence is far from satisfactory. Special interest therefore attaches itself to the report of an outbreak of typhoid fever due to infected ice. The outbreak, which

occurred in Elmira, N. Y., during the summer of 1923, included 37 cases. CONWAY (*Am. Jour. Pub. Health*, 1924, **16**, 574) believes that in view of the facts presented there seems little doubt that the outbreak of typhoid was directly due to the consumption of the superficial layer of natural ice, harvested from the heavily polluted Chemung River, even though stored, as it was, for a period of from five to six or possibly seven months. He also warns against the use of iced drinks chilled with ice harvested from polluted sources, even though subject to several months' storage.

Effect of Fatty Acids on the Resistance of Mice to Transplanted Cancer.—NAKAHARA (*Jour. Exper. Med.*, 1924, **40**, 363) declares that sodium oleate, oleic acid, linolic acid and linolenic acid injected into mice in suitable amounts induce a material increase in the resistance against subsequent transplantation of cancer grafts, although they fail to exert so marked an influence or cancer grafts already in place. Sodium palmitate and sodium stearate, on the other hand, do not produce immunity, at least in the amounts employed in the present study.

Immunity in Rocky Mountain Spotted Fever.—CONNOR (*Jour. Immunol.*, 1924, **9**, 269) contrasts the behavior of the virus in the tick and in laboratory animals. He states that the fact that there are so few organisms in the blood may be the reason why the virus in this situation is not amenable to attenuation. In tick tissues and in the tissues of guinea-pigs the virus may be attenuated by drying in the cold, and after keeping for from five to thirty days at a below zero temperature the tissue is no longer virulent, but will produce immunity. The most effective method of using combinations of virus and immune serum seems to be where virus is given in rather large dose and allowed to grow for twenty-four hours when a dose of serum is given to stop the infection. Another method which is successful under limited conditions is the giving of large doses of mixtures of virus and serum. An immunity may be achieved which equals that following an attack of the disease. The same mixtures heated to 60° for twenty minutes have been ineffective. The virus-serum mixtures are applicable for the present to guinea-pigs only. It is questionable whether the same amount of immune serum which will protect a guinea-pig will do the same for a larger animal. A virus that is much more concentrated is desirable, and one that may be calculated as to its minimum infectious dose prior to administration. The fact that immunity depends only on the amount of virus given is brought out, the immune body having nothing to do with the production of immunity in another animal.

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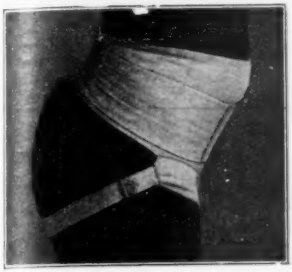

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"When a mixture of ground roasted Coffee and water is brought to the boiling point, a vigorous ebullition takes place. While beginning at lower temperature this obvious effervescence becomes marked at a temperature of about 96 degrees to 98 degrees C. and continues for from one to two minutes, the temperature never rising above 102 degrees C. A gas is given off.

"Examination showed that this gas consisted almost entirely of carbon dioxide, but that minute amounts of other gases, sometimes with the characteristic disagreeable odor of decaying vegetable matter, are present, as well as traces of aromatic compounds of a distinct almond odor.

"Further examination showed very small quantities of carbon monoxide, presumably absorbed by the bean during the roasting process. For all practical purposes, however, the gas may be regarded as almost exclusively carbon dioxide.

"At this point it may be desirable to point out a few facts relative to the part carbon dioxide plays in the economy of nature in order to dispel or counteract the thought that this gas is only the result of objectionable processes and therefore harmful.

"It was formerly supposed that carbon dioxide was a poison. We now know that such is not the case; in fact, that without this gas the building up of sugar and other food substances in nature would be impossible.

"Carbon dioxide tends to restrain the action of many kinds of microorganisms in foods, and to prevent the undesirable oxidations of certain types of fats, and is therefore of large and growing importance in the preparation and preservation of many food materials.

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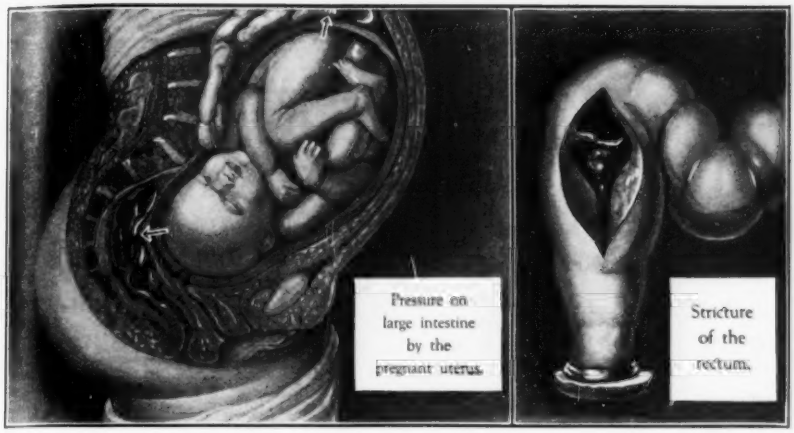

Constipation in Pregnancy

As you know, at least half the cases are subject to constipation due to pressure of the uterus and loss of tonicity of the abdominal walls. Consequent straining at stool leads to hemorrhoids.

Lesions accompanying eclampsia, vomiting in pregnancy and acute yellow atrophy of the liver are all influenced by bowel conditions. Furthermore, toxins from constipation put an additional strain upon the kidneys.

The health of both mother and child are jeopardized by the indiscriminate use of catharses. Saline catharses deplete the system of body fluids and are particularly harmful in pregnancy. Cathartics which act through initiating peristalsis may even lead to abortion.

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By. F. A. Upsher Smith, Ph. C.

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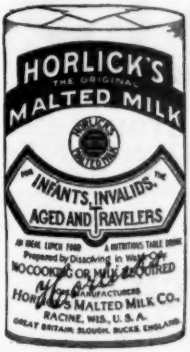

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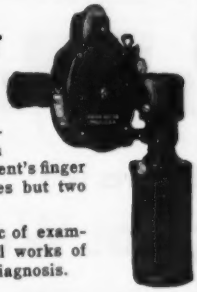

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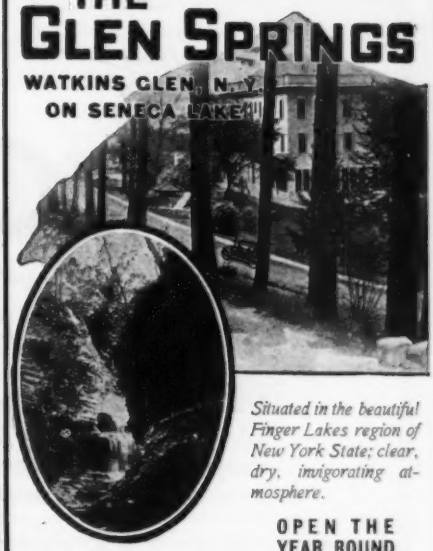

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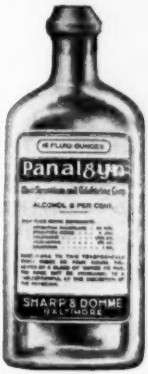

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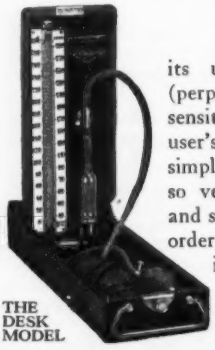

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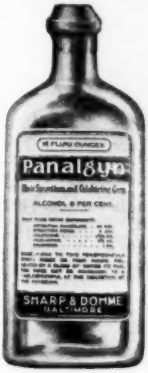

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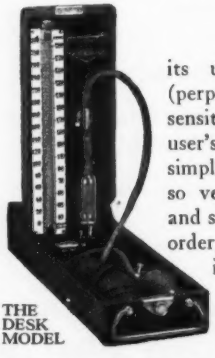

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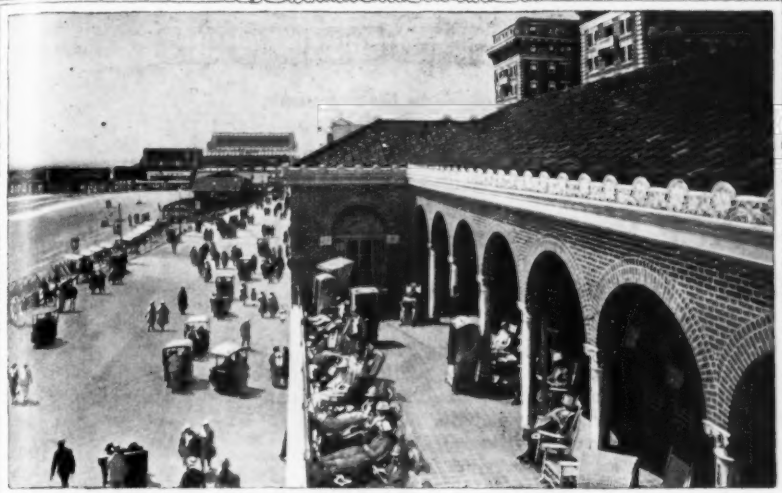

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